THE COLLAGEN CURE

LOOK YOUNGER
FEEL BETTER
GET STRONGER
RECOVER FASTER

DR. JAMES DINICOLANTONIO
AND SIIM LAND

The Collagen Cure

The Forgotten Role of Collagen and Glycine for Optimal Health and Longevity

Dr. James DiNicolantonio

Author of The Salt Fix

&

Siim Land

Author of Metabolic Autophagy

2022

DISCLAIMER

Text Copyright © James DiNicolantonio and Siim Land 2022

All rights reserved. No part of this guide may be reproduced in any form without permission in writing from the publisher except in the case of brief quotations embodied in critical articles or reviews.

Legal & Disclaimer

The information contained in this book is not designed to replace or take the place of any form of medicine or professional medical advice. The information in this

book has been provided for educational purposes only.

The information contained in this book has been compiled from sources deemed reliable, and it is accurate to the best of the authors' knowledge; however, the authors cannot guarantee its accuracy and validity and cannot be held liable for any errors or omissions. Changes are periodically made to this book. You must consult your doctor or get professional medical advice before using any of the suggested remedies, techniques, or information in this book.

Upon using the information contained in this book, you agree to hold harmless the

authors and publisher from and against any damages, costs, and expenses, including any legal fees potentially resulting from the application of any of the information provided by this guide. This disclaimer applies to any damages or injury caused by the use and application, whether directly or indirectly, of any advice or information presented, whether for breach of contract, tort, negligence, personal injury, criminal intent, or under any other cause of action.

You agree to accept all risks of using the information presented inside this book. You need to consult a professional medical practitioner in order to ensure

you are both able and healthy enough to participate in this program.

All rights reserved. No part of this publication may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of the publisher, except in the case of brief quotations embodied in critical reviews and certain other noncommercial uses permitted by copyright law. For permission requests, contact the publisher, at the addresses http://drjamesdinic.com/ or http://www.siimland.com.

Jacket design by James DiNicolantonio and Siim Land

Table of Contents

Disclaimer

Table of Contents

About the Authors

Preface

Introduction

Chapter 1: All About Collagen

Chapter 2:Glycine and the Origin of Life

Chapter 3: The Short and Sweet on Glycine

Chapter 4: Collagen for Joints, Tendons, Osteoarthritis & Osteoporosis

Chapter 5: Cardiovascular Disease: The Vitamin C-Collagen Connection

Chapter 6: Collagen and Glycine for the Brain

Chapter 7: Exercise and Collagen Health

Chapter 8: The Full Collagen Cure Plan

Conclusion

References

About the Authors

Dr. James DiNicolantonio

As a cardiovascular research scientist and Doctor of Pharmacy, Dr. James J. DiNicolantonio has spent years researching nutrition. A well-respected and internationally known scientist and expert on health and nutrition, he has

contributed extensively to health policy and medical literature. Dr. DiNicolantonio is the author of 6 best-selling health books, The Salt Fix, Superfuel, The Longevity Solution, The Immunity Fix, The Mineral Fix and WIN.

His website is www.drjamesdinic.com. You can follow Dr. DiNicolantonio on Twitter and Instagram at @drjamesdinic and Facebook at Dr. James DiNicolantonio.

He is the author or co-author of more than 300 medical publications, including several high-profile articles related to nutrition, including a December 2014 opinion piece about sugar addiction in

The New York Times that was the newspaper's most emailed article during the 24 hours following its publication. Dr. DiNicolantonio has testified in front of the Canadian Senate regarding the harms of added sugars and serves as the Associate Editor of British Medical Journal's (BMJ) Open Heart, a journal published in partnership with the British Cardiovascular Society. He is also on the Editorial Advisory Board of several other medical journals, including Progress in Cardiovascular Diseases and International Journal of Clinical Pharmacology & Toxicology.

Siim Land

Siim Land is an author, speaker, content creator and renown biohacker from Estonia. Despite his young age, he is considered one of the top people in the biohacking and health optimization

community with thousands of followers worldwide. Siim Land has written books like Metabolic Autophagy, Stronger by Stress, The Immunity Fix, The Mineral Fix and WIN. His website is www.siimland.com. You can follow Siim on Instagram @siimland and as Siim Land on YouTube.

Siim started researching and doing self-experiments with nutrition, exercise, and other strategies to improve his performance and health after high school when he enrolled in the military for a year. He then obtained a bachelor's degree in anthropology in Tallinn University and University of Durham in the UK. By now he has written several

books about diet, creates content online, and keeps himself up to date with the latest knowledge in science.

Preface

A note from Dr. DiNicolantonio:

In my previous books, The Salt Fix, WIN and The Obesity Fix, I tackled how to improve overall health, athletic performance, and weight loss. The Collagen Cure builds on these works by exploring the story of collagen, which just so happens to be the most abundant protein in your body.

Collagen is near and dear to my heart because at the age of 26 I partially tore my pectoralis major tendon while bench pressing. I never had surgery to get it repaired, although in hindsight I should have. After my injury, I began

researching how nutrition affected tendon health and discovered the importance of collagen. After the injury, I was only able to bench press 5-pound dumbbells, a far cry from the 50-pound dumbbells I was used to lifting. In other words, I lost 90% of my bench press strength after my injury. Slowly over time I increased the strength of my pectoralis tendon.

In this book, you will learn strategies to increase the strength and health of not only your tendons, but also your bones, muscles, joints, and ligaments. In addition, you will learn how to improve your hair, skin, and nail health. You will also learn about the 4-billion-year-old

story of the smallest amino acid that makes up collagen, glycine, which was one of the first substances that sparked life on Earth. Lastly, you will learn about the benefits of collagen and glycine, the optimal dosing of each for numerous health conditions, the factors that weaken and strengthen collagen, what are the best and worst collagen supplements, and we will also provide you with a dietary and exercise plan to maximize your collagen health. The Collagen Cure is a labor of love. I have poured several years of research into this book providing hundreds of references so that you can have one easy resource to guide you towards

optimal collagen health. Let the healing begin!

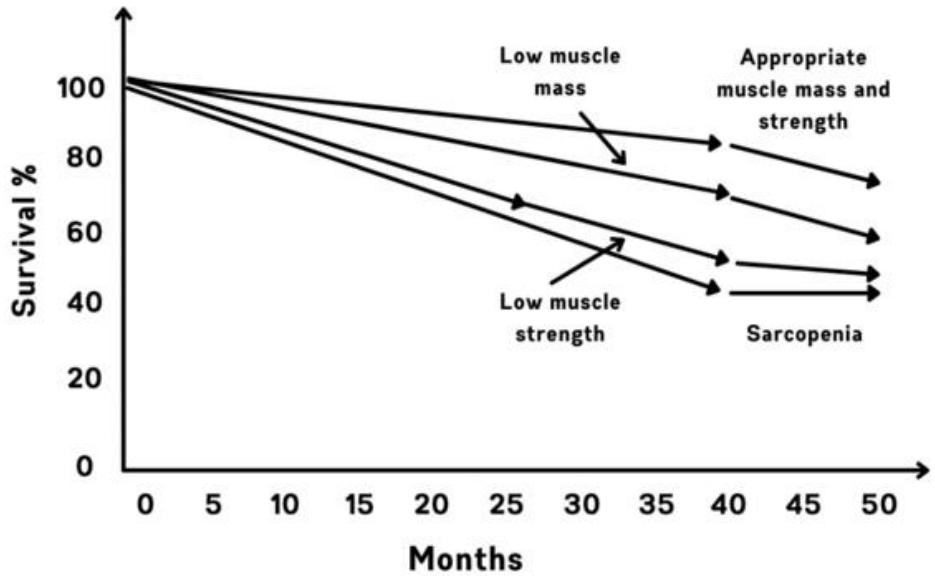
Introduction

The quest to slow down and reverse aging is a big part of modern culture and the industrialized world. In 2020, the global anti-aging consumer product market was valued at $58.5 billion U.S. dollars and is estimated to grow 7% per year between 2021 and 2026[1]. If you were to account for all the other longevity-focused healthcare and biomedicine companies, that number would be up to $25 trillion[2]. Collagen protein is a very popular and a commonly referenced anti-aging supplement that,

as of 2021, has a market value of $9.75 billion and is expected to surpass $20 billion by 2030[3]. The reason for the tremendous interest in collagen is because numerous studies have found that supplementing with collagen can reduce wrinkles, improve overall skin health, reduce joint pain, and increase bone mineral density[4],[5],[6],[7].

When most people think of protein, the first thing that generally comes to mind is building muscle. It's true that dietary protein is extremely important for muscle growth and overall health. Indeed, not getting enough protein (as well as lack of lifting weights or exercise in general) can

lead to something called sarcopenia or age-related muscle loss. You might think – *So what? I'm not a bodybuilder.* However, **the average person loses around 1% of their muscle mass per year after the age of 30**[8],[9],[10],[11]. That means that by the time you are 80, you will have lost around 50% of your muscle mass! If you're still not concerned, there **is a lot of evidence showing that greater muscle mass and strength are associated with reduced risk of all-cause mortality**[12], [13],[14]. In other words, having more muscle, especially as we age, is associated with living longer.



Adapted From: Isoyama et al (2014)

Besides a higher risk of death, lack of muscle mass predisposes you to multiple chronic degenerative diseases, such as type-2 diabetes, insulin resistance, cardiovascular disease, metabolic syndrome, and arthritis[15],[16],[17],[18],[19]. This is because skeletal muscle is the largest

glucose sink in the body, helping to soak up the glucose that comes from our diet. Furthermore, **insulin resistance typically first occurs in the skeletal muscle, and then tends to spill over to the liver and other organs**. Thus, if you can maintain a healthy muscle mass, you may maintain insulin sensitivity and optimal blood glucose control. Additionally, muscle also burns 2-3 times more calories than fat mass, making it very beneficial for weight loss[20]. Not only that but simple tasks, such as carrying out the garbage, or lifting a gallon of milk, may no longer be an option (not to mention taking the stairs, walking without a cane and playing with

your grandchildren). Thus, a lack of muscle mass can not only make you sick, but it can prevent you from doing the things you want to later in life.

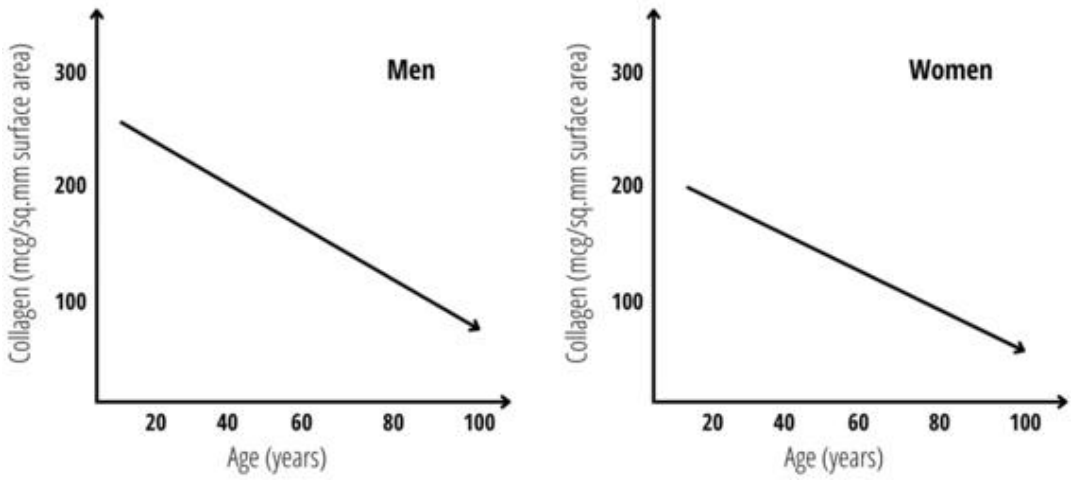
For preventing age-related muscle loss and frailty, we need to keep exercising with resistance training and consuming adequate amounts of protein[21],[22],[23],[24],[25],[26],[27]. However, there is another type of protein that we are losing from our bodies as we age and that protein is known as collagen. **Collagen is the most abundant protein in the human body making up approximately 30% of all your protein by mass[28],[29].** It makes up your hair, teeth, skin, nails,

organs, arteries, cartilage, bones, tendons, and ligaments (just to name a few)[30]. Collagen is literally "*the glue that holds you together*" or *"glue producer"* derived from Greek. Thus, **losing collagen may be more important than losing muscle as you age.** In fact, the loss of collagen can start a full decade prior to the loss of muscle. **Starting at the age of 20, you lose just under 10% of your skin's collagen content every decade**[31]. Thus, by the time you are 75 years old you would have lost 50% of your skin's collagen content! The density of collagen in the skin also drops starting at the age of 20 by about 8% per

decade[32]. Thus, by the time you are 80 you may have lost 50% of your collagen density. This loss of collagen, both total content and density, is primarily why skin becomes thinner with age. Essentially, **you can think of aging as a collagen deficiency.** And if you want to keep your skin, organs, arteries, tendons, ligaments, bones and so on, strong, and healthy you need to maintain good collagen health and prevent the steady decline of collagen that occurs with aging.

Skin collagen content decline with age

(~ 50% loss by the age of 75)



Adapted From: Shuster et al (1975)

Women have less collagen than men at all ages but the rate of decrease in collagen is nearly identical in both sexes.

Why does a loss of collagen with age matter?

- Do you have knee pain? Collagen makes up your cartilage, which is what protects your joints by preventing bone rubbing against

bone[33],[34]. In other words, **joint pain and osteoarthritis can be caused by a deficiency in collagen**.

- The amino acid **glycine**, which makes up every third amino acid in collagen, **is a rate limiting factor in the formation of our bodies most potent endogenous antioxidant called glutathione**[35]. Thus, any inflammatory condition can be worsened, or potentially caused by, a deficiency in glycine, which is found in collagen.
- Have you noticed that your skin has more wrinkles, brown spots, or

has lost its elasticity and youthfulness? Do you have burns and wounds that don't heal? That could be a collagen deficiency[36], [37],[38].

- Do you have osteoporosis? It turns out that **half your bone is made of protein with most of that protein being composed of collagen**[39]. In other words, **a deficiency in collagen can lead to weaker bones**[40],[41],[42].

Are you starting to get the picture for why collagen is so important for health? Since collagen also helps make up your organs

(kidney, liver, and heart for example), tendons, ligaments, arteries, vertebrae, etc., **almost any condition can be worsened or caused by a deficiency in collagen.** In fact, the dramatic rise in diseases such as osteoporosis, tendon ruptures, degenerative disks, and osteoarthritis are thought to be due to, or contributed by, collagen deficiency[43],[44],[45].

So why do we lose so much collagen as we age? One of the main reasons is because we don't get enough glycine. Glycine is the smallest of all the amino acids and our body endogenously makes about 3 grams of it every day[46].

It is considered a non-essential amino acid because we can synthesize it[47]. However, it should be considered a 'conditionally essential' amino acid because **we don't make enough glycine to support adequate collagen production**[48]. The reason is because when the glycine synthesis pathway first evolved in smaller mammals it never improved with increasing mammalian size[49],[50]. In other words, **any mammal that is over 88 pounds doesn't synthesize enough glycine to support optimal collagen health**[51]. This is perhaps why osteoarthritis has been detected in the skeletons of large

dinosaurs from the Jurassic Age (100-150 million years ago) and in large mammals like elephants and rhinoceroses and in great apes, chimpanzees, gorillas, and bonobos in both the wild and in captivity[52]. Osteoarthritis has even been found in Neanderthals, Upper Paleolithic, and Neolithic human fossils and in human fossils of the Middle Pleistocene in Spain[53]. **When it comes to modern day humans, we may need to supplement with an additional 10 grams of glycine or more** (in addition to the 3 grams we synthesize and the 3 grams we consume in our diet) **for**

optimal collagen health[54]. This is the difference between surviving and thriving. If you want your body to thrive, then you want ***optimal*** collagen synthesis and that requires consuming more glycine than what the body makes.

People who don't get an optimal amount of glycine per day won't die because our body makes enough to live (hence it being a non-essential amino acid), but the body adapts to suboptimal glycine intake by decreasing collagen turnover. This decrease in collagen turnover leads to a degeneration in our collagen health via an increase in the oxidation, glycation, and unnatural cross-linking of

collagen[55]. This is an example of how not getting enough of a non-essential substance doesn't kill you, but there is a cost, and that cost is weaker collagen. In other words, **not getting optimal amounts of glycine (and/or collagen) in the diet leads to weaker collagen, accelerated aging and degenerative diseases.**

This book will walk you through everything you need to know about collagen and glycine. We're going to cover the health benefits of both and how to obtain them in the right amounts for optimal longevity, vitality, and anti-aging. It will also teach you how to improve your

overall collagen health via diet, supplements, biohacking techniques and lifestyle.

Chapter 1: All About Collagen

Collagen has been around as long as animals have been alive (about 580 million years)[56],[57]. It is found in numerous species, anywhere from freshwater sponges and sea urchins, to fish and higher mammals[58]. Collagen is the most abundant protein in animals and humans making up bones, skin, hair, teeth, muscle, cartilage, organs, tendons, ligaments, intestines, and arteries. **In fact, 70% of the protein in your skin is made up of collagen[59].** Collagen is what gives skin its firmness, elasticity,

and strength. Slightly more than 50% of all collagen in the body is found in the skin, 40% in bone, and most of the remainder is found in tendons and ligaments[60]. **Wrinkles, sagging skin, and skin spots are all indicators of poor collagen health.** Besides skin appearance, poor collagen health is hard to recognize because it's happening inside your body. This is why so many people don't recognize the importance of collagen but hopefully this book will change that.

Our human ancestors used to consume more collagen because they would eat the entire animal (organs, skin, bone

marrow, cartilage, etc.), which is rich in collagen[61],[62],[63]. Even compared to a few hundred years ago we now consume less collagen. Our grandparents used to cook the entire animal, including the bones and collagenous tissues, in a pot making soups and stews. The broth would be filled with collagen. You could tell how rich these broths and stews were in collagen because the gelatin would solidify once placed in the refrigerator. **That's how you know you have a good collagen stew, when there is a lot of gelatin that forms once the broth is placed in the refrigerator.** Bone broth that does not form this gelatin will not provide a reliable amount of collagen

precursors.[64] Consuming tendons, ligaments and skin is a source of collagen, something which the average person no longer consumes. Back 100 years ago, when it came to food, nothing went to waste. We appreciated the value of the whole animal with all parts being used. However, nowadays our intake of collagen has dramatically gone down. Instead of eating the entire animal, we now consume boneless, skinless chicken breasts, skinless fish, and throw out all the collagen-rich parts of the animal. This places us in a state of collagen deficiency. Additionally, numerous chronic diseases, medications and

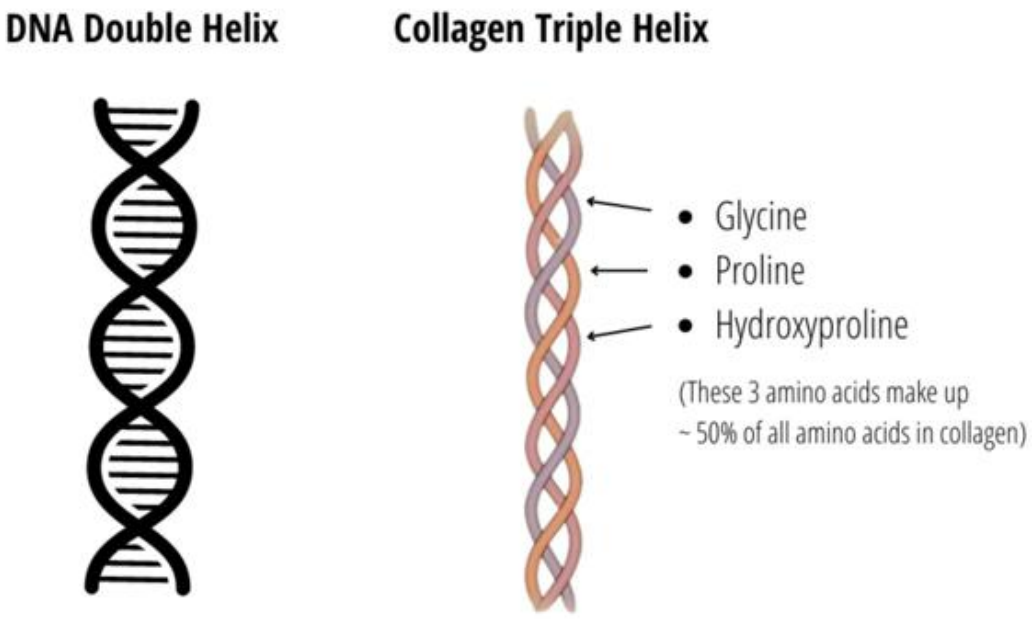
inflammation damage our collagen health.

Types of Collagens

There are at least 29 different types of collagen in the human body[65],[66]. However, they are all composed of a repeating triple amino acid chain, GLY-X-Y, with GLY indicating glycine and X and Y being any of the 20 amino acids but are typically proline and hydroxyproline[67]. Glycine, proline, and hydroxyproline make up around 50% of the amino acids in collagen[68]. This is what makes collagen unique compared to other proteins. These repeating amino acid chains form longer polypeptide chains, with three chains becoming wound together into a triple helix to form

collagen. You may ask yourself, *“What is a triple helix?”* Well, if you remember pictures of DNA, then you already know what a *double helix* is - two strands wound together. Collagen is a *triple helix*, or three strands of polypeptides wound together. This is what gives collagen its tensile strength. Like that of a winding rope, the twisting of the polypeptide chains is what makes collagen strong. The three polypeptide chains that make up collagen can either be identical (called homotrimers) or a mixture of two or three distinct chains (called heterotrimers)[69]. Each polypeptide chain contains around 1,000 amino acids

but can range anywhere from 662 to 3,152 amino acids[70].



There are three different groups of collagens (with many different types of collagen making up each group)[71]. They include:

- **Fibrillar collagens** (Type I, II, III, V, and XI)

- **Fibril-associated collagens** (IX, XII, XIV)
- **Non-fibrillar collagens**, which include the sheet formers (IV, VIII), beaded filaments (VI), anchoring fibrils (VII), growth plate-specific (X) and others

The names of these types of collagens reflects the order in which they were discovered. Fibrillar collagens form banded uninterrupted fibrils. Fibrillar collagens make up extracellular matrix proteins which is conserved in all multicellular animals[72]. These fibrillar collagens are important for forming bone and teeth. Collagen molecules provide

supportive extracellular scaffolding and interaction sites for cells and macromolecules. Fibril-associated collagens with interrupted triple helices are a group of collagens in which collagenous domains are interrupted by non-collagenous sequences. Type IX, XII, XIV, XV, and XVIII contain glycosaminoglycan chains, such chondroitin sulfate and/or heparan sulfate chains, and are also considered proteoglycans.

The five most common types of collagen (and where they are found in the body)[73]**:**

- **Type I**: skin, tendons, vasculature, organs and bones
- **Type II**: cartilage
- **Type III**: skin, large blood vessels, uterus, and intestines
- **Type IV**: basement membranes (capillaries, kidney, eye lense, skin and liver)
- **Type V**: cell surfaces, hair and placenta

Now that you understand how complex collagen is, let's skip the scientific jargon and get more to the point. What you need to know is that there are many types of collagen and they are quite complex. Of the 29 types of collagen, **Type I, II, and III are the most**

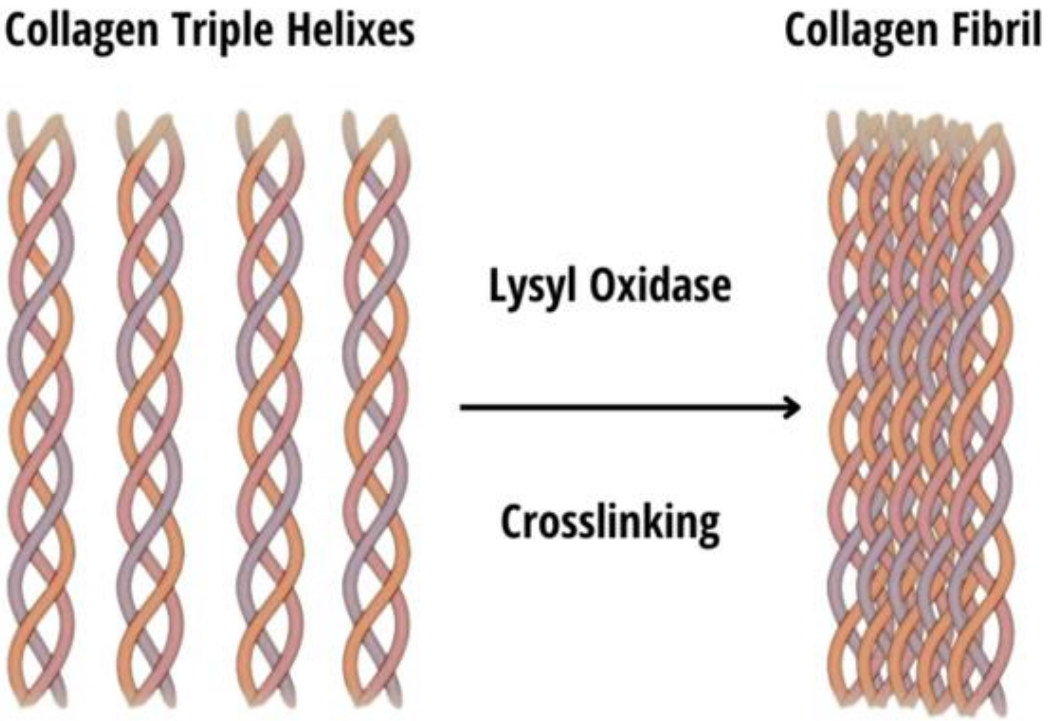
abundant, making up around 80-90% of the total collagen in our body[74].

Type I collagen is found in your skin, hair, nails, tendons, ligaments, and bones. Gram for gram, Type I collagen is stronger than steel (*let that sink in*). If you are a Lord of the Rings fan, you can think of Type I collagen like Mithril (Dwarvish armor). It makes up 95% of the entire collagen content of bone and approximately 80% of the total protein in bone[75]. Of course, collagen is much lighter than steel, so it's not as if you could cut a piece of steel easier than Type I collagen – if that were the case then no one would ever get tendon or

ligament injuries. However, if provided collagen and steel at the same weight, Type I collagen would be stronger than steel.

The reason why Type I collagen is so strong is because 96% of it is made up of the triple helix, whereas Type XII collagen for example, is composed of less than 10% triple helix[76]. **It's the triple helix, the winding together of the three polypeptide chains that gives collagen its strength**. Collagen's triple helix structure guards it from being broken down by enzymes[77]. Additionally, Type I collagen has another property giving it extra strength. Indeed,

its triple helixes are covalently cross-linked to one another using the copper-dependent enzyme lysyl oxidase (LOX) [78],[79]. Think of Type I collagen like a rope, with all its twisting strands, but then imagine someone connecting those strands of rope together like chain link fence. That is basically what lysyl oxidase does to form Type 1 collagen - it makes Type I collagen become *"super-collagen"*. So, **if you are not ingesting optimal amounts of copper** (as well as vitamin C, sodium, and many other nutrients) **then your Type I collagen will not be as strong.**



Type II collagen is found in your cartilage and **Type III collagen is found in your arteries, intestines, and for women, their uterus**. Type IV collagen makes up the glomeruli (filtering units) of the kidney, and it also makes up your capillaries. **Thus, if you want healthy arteries and capillaries, and good blood flow throughout your body, you**

need good collagen health. This is likely why taking collagen supplements have been found to improve blood pressure and arterial stiffness[80]. While we won't go into detail about all the other types of collagens, there are many others that make up your teeth, eyes, and organs. Since collagen makes up your organs and tissues, a deficiency in collagen can lead to negative health consequences in those areas of the body. **The below table summarizes the types of collagen and their locations in the human body**.

Types of collagens and their locations in the body (Adapted from[81])

Type	Location/Notes
I	Skin, artery walls, cornea, tendons, bones, teeth
II	Makes up 50% of all cartilage protein
III	Artery walls, skin, intestines, and uterus
IV	Capillaries, glomeruli of the kidney, eye lens and skin
V	Interstitial tissue
VI	Interstitial tissue
VII	Dermoepidermal junctions
VIII	Some endothelial cells
IX	Associated with type II and

	XI fibrils
X	Hypertrophic and mineralizing cartilage
XI	Cartilage
XII	Interacts with type I collagen and glycosaminoglycans
XIII	Transmembrane collagen, interacts with fibronectin and other components of basement membranes
XIV	Known as undulin
XV	-
XVI	-

XVII	Transmembrane collagen
XVIII	Source of endostatin
XIX	FACIT collagen (a proteoglycan)
XX	-
XXI	FACIT collagen (a proteoglycan)
XXII	-
XXIII	MACIT collagen (membrane-associated collagen with interrupted triple-helices)
XXIV	-
XXV	-

XXVI	-
XXVII	-
XXVIII	-
XXIX	Epidermal collagen (some consider this collagen part of Type VI) and not a truly different type of collagen

Collagen Synthesis

Your body can make its own collagen, but it needs the building blocks (mainly glycine, hydroxyproline and proline) to do so. Additionally, **consuming collagen peptides leads to the absorption of many of these peptides intact, which can directly stimulate collagen synthesis and these peptides can even accumulate in cartilage**[82]. Thus, taking collagen supplements provides both the amino acids and peptides to help build collagen, which are lacking in our diet, and it also stimulates collagen production.

The cells that make collagen in your body include:

Bone cells (osteoblasts)

Skin cells (fibroblasts)

Cartilage cells (chondrocytes)

Dental cells (odontoblasts and cementoblasts)

Retinal cells (Müller cells) and others

Vitamin C stimulates messengerRNA (mRNA) in the above cells to initiate collagen synthesis[83]. **A deficiency in vitamin C results in inadequate collagen synthesis** and scurvy (hence bleeding gums)[84]. It usually takes

several months of little to no vitamin C intake for clinical symptoms to present. Procollagen gets modified by the addition of hydroxyl groups to proline and lysine, a process that requires vitamin C to form collagen.[85],[86] This process consumes one ascorbate (vitamin C) molecule per hydroxylation[87]. For proline and lysine to be hydroxylated, vitamin C needs to reduce the inactive form of iron (Fe^{3+} or ferric iron) into its active form (Fe^{2+} or ferrous iron)[88]. Thus, iron is also important for collagen synthesis. Copper is also important for moving and storing iron throughout the body[89]. Vitamin A is important for moving copper around the

body[90]. Thus, inadequate vitamin C, iron, copper or vitamin A can reduce collagen synthesis/strength. Here's an overview of the entire process.

Below is a brief overview of the steps in collagen synthesis[91].

Intracellular steps – Begins inside the cell that is synthesizing collagen.

Formation of Pro-alpha chains (procollagen, a precursor of collagen) in the rough endoplasmic reticulum.

Hydroxylation – hydroxylation of proline and lysine (a vitamin C-dependent process).

Glycosylation – Some hydroxylysine gets modified by glycosylation (with galactose or galactosyl-glucose).

Assembly – Formation of disulfide bonds to assist in connecting and forming the three polypeptide molecules of the triple helix.

Secretion – The procollagen molecules are translocated to the Golgi apparatus where they are packaged into secretory vesicles, fusing with the cell membrane, and releasing the procollagen molecules into the extracellular space. This process is also dependent on vitamin C.

Extracellular steps – what occurs outside the cell to form mature collagen

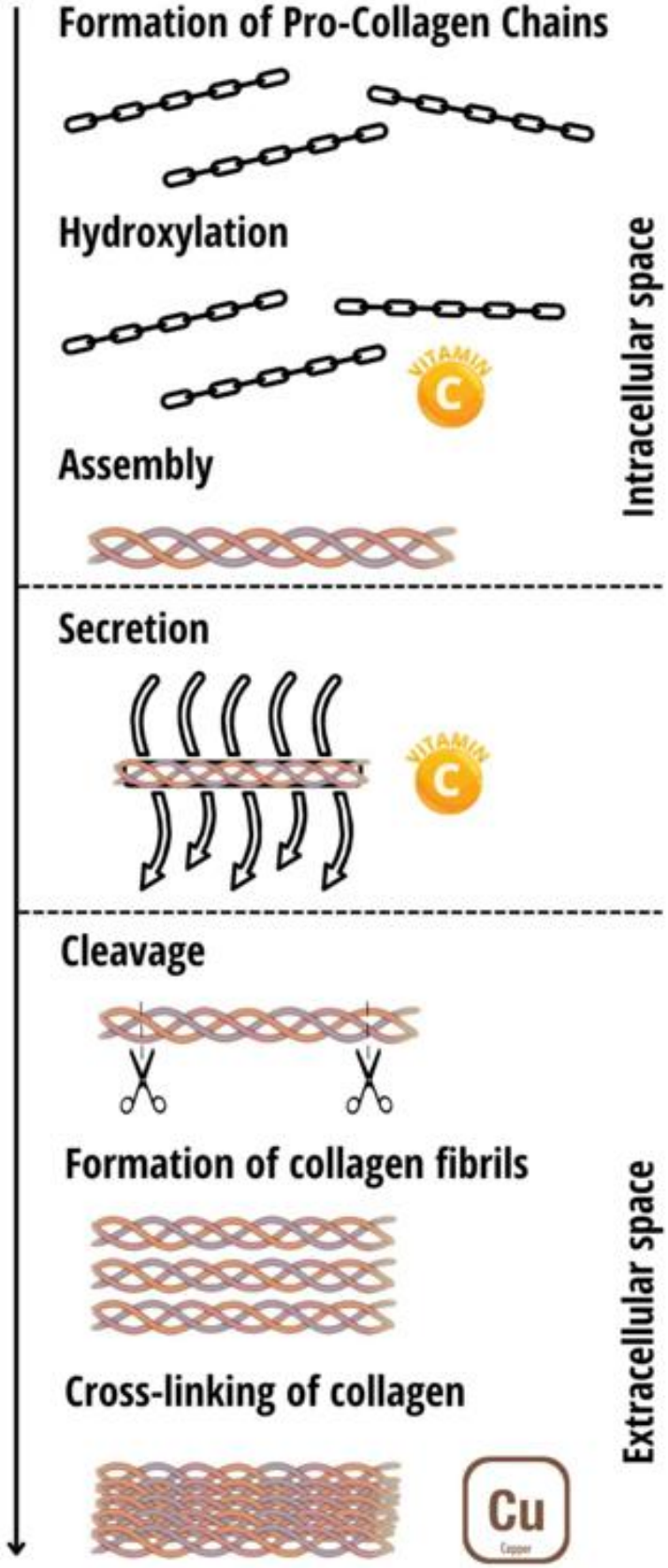
molecules

Cleavage of amino and carboxyl terminal pro-peptides – Extracellular enzymes called procollagen aminoproteinase and procollagen carboxyproteinase remove the extension peptides from the amino and carboxyl terminal ends releasing the triple helical collagen molecules

Formation of collagen fibrils – The released triple helical collagen molecules, approximately 1,000 amino acids per chain, assemble into collagen fibers. The fibrils are then stacked together to forming banded fibers in connective tissues.

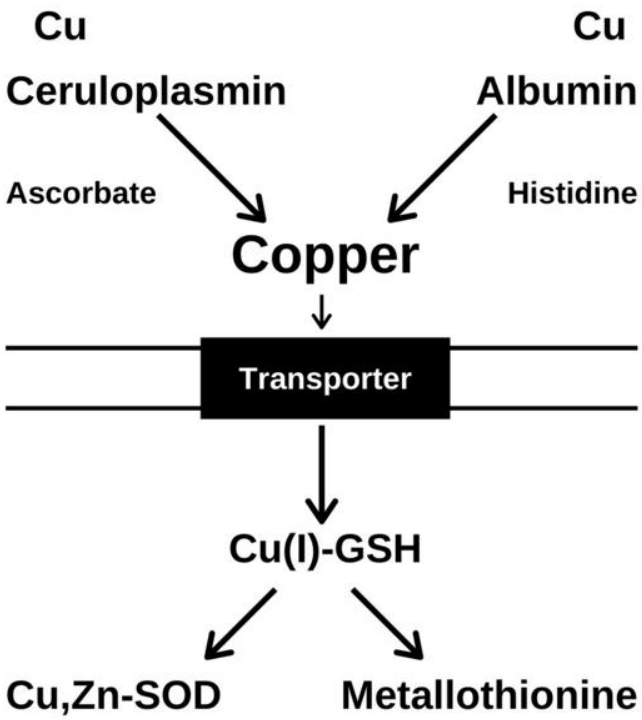
Cross-linking of collagen – The collagen fibers are stabilized via covalent cross-links both within and between the triple helical units. This cross-linking occurs via lysyl oxidase, a copper-dependent enzyme, which deaminates certain amino groups of lysine and hydroxylysine residues yielding aldehydes helping to form stable covalent cross-links important for the tensile strength of collagen fibers. Histidine may also be involved in certain cross-links. **Lysyl oxidase needs copper to be in its reduced, cuprous form, and this requires vitamin C.** Essentially, lysyl oxidase is dependent on both copper and vitamin C. The

movement of copper around the body requires vitamin A. Thus, vitamin A and C are important for collagen health.


Formation of Pro-Collagen Chains
Hydroxylation
VITAMIN
C
Assembly
Intracellular space
Secretion
VITAMIN
C
Cleavage
Formation of collagen fibrils
Cross-linking of collagen
Cu
Copper
Extracellular space

Vitamin C can have a positive or negative effect on copper metabolism. **If you take vitamin C with copper, or up to 75 minutes prior to copper, it reduces copper absorption**. However, if you take vitamin C after copper ingestion (75 min later), it increases ceruloplasmin and lysyl oxidase activity, and improves the delivery and utilization of copper. **In other words, take vitamin C about 75 minutes or more after you ingest copper.** Vitamin C helps to shuttle copper ions into cells by releasing the attached copper ions from ceruloplasmin (the main carrier of copper in our blood)[92]. Histidine, an amino acid,

helps with the transport of copper from albumin into cells[93]. Glutathione, which you can increase with supplemental n-acetylcysteine and glycine, helps to facilitate the transfer of copper to metallothionine and superoxide dismutase.



Source: DiNicolantonio and Land (2021) 'The Mineral Fix'

Based on this, **some of the symptoms of vitamin C deficiency may also be due to *copper deficiency***. *Furthermore, both copper and vitamin C are important* for collagen health. Thus, there is likely a combination of several deficiencies occurring simultaneously when someone has poor collagen health. Indeed, **copper deficiency in animals, which causes bone and connective tissue defects, anemia, and subcutaneous hemorrhaging mimics that of scurvy.** Coiled hairs, which can be found in copper deficiency, called Menkes steely hair syndrome, can also be found in some patients with scurvy. Thus, it's

possible that copper deficiency is caused by vitamin C deficiency and is playing some role in the symptoms of scurvy. Essentially, **scurvy may be a vitamin C and copper deficiency syndrome**.[94]

The Importance of Sodium for Vitamin C Transport and Collagen Health

Sodium is what allows us to absorb vitamin C and drives vitamin C into virtually all tissues in the body, including the skin, bone, brain, adrenal glands etc. via the SVCT transporters (sodium-dependent vitamin C transporters)[95],[96]. This process needs two sodium ions to absorb one ascorbic acid molecule. **Low sodium levels in the body or blood reduce vitamin C transportation into the tissues where you need vitamin C to make collagen.** Hyponatremia (low sodium in the blood)

can also worsen bone health by causing vitamin C deficiency. In animal studies, hyponatremia decreases the activity of the sodium-dependent vitamin C transporter, reducing the uptake of vitamin C into the bone, raising oxidative stress, and inducing bone loss[97]. These harmful effects are due to a decrease in bone and collagen health because vitamin C is crucial as an antioxidant and for collagen synthesis[98]. Considering that vitamin C deficiency is more common than thought[99], following a low salt diet can worsen an already suboptimal vitamin C status. Ironically, **having a low vitamin C (or vitamin E)**

intake can lead to sodium wasting even during sodium deficiency[100], [101]. This is because vitamin C helps with the synthesis of the sodium-retaining hormone aldosterone. Vitamin E also protects the adrenal glands from oxidative stress and having a low vitamin E intake seems to reduce aldosterone release causing greater sodium losses during sodium deficiency. In other words, **having a low vitamin C or vitamin E intake or status may increase the risk of sodium deficiency.**

But does low sodium status affect bone health negatively?

Balance studies show that **low sodium intakes** (even up to 2,200 mg per day) **lead to:**

1.) Negative sodium balance

2.) Sodium, calcium, and magnesium being stripped from bone and

3.) Negative calcium and magnesium balance[102],[103],[104].

In essence, **low salt diets can deplete your sodium, calcium, and magnesium levels in the body**, which worsens bone mineral density and increases the risk of osteoporosis. The Women's Health Initiative (WHI), a prospective study on 4,000 post-menopausal women, concluded that,

"Higher levels of sodium intake…were associated with significantly fewer hip fractures."[105]. The authors also wrote that **a low salt diet can increase the production of osteoclasts**, which are **cells that break down bones**, by raising stress hormones such as renin and aldosterone. In the study, there was an association between *higher* bone mineral density and *greater* salt intake. **Participants who were consuming more than average amount of salt had higher bone mineral density and a lower risk of fractures.** Thus, the evidence suggests that consuming more salt, not less, benefits the bones.

Low sodium status may also promote cognitive decline because of vitamin C deficiency in the brain. Chronic moderate hyponatremia in rats impairs their memory and correcting the hyponatremia fixes the memory impairment[106]. A low salt diet can also directly predispose you to vitamin C deficiency by decreasing vitamin C absorption in the intestine[107]. That's right; **vitamin C absorption in our body depends on sodium.**

Contrary to what we've been told, the evidence suggests that consuming more salt, not less, is good for our bones. For decades the unintended consequences

of population-wide sodium restriction have been conveniently swept under the rug. For the sake of your bones and your mind, you should think twice before blindly following the low-salt advice. Your body, and your brain, may thank you for it.

What Breaks Down Your Collagen?

In the 21st century, we are facing an onslaught of oxidative stress, which in excess can worsen our health and accelerate aging[108]. Consider this, more than 90% of the global population breaths polluted air[109]. In fact, breathing polluted air ranked #6 (ambient particulate matter) and #8 (household air pollution) in 2016 as leading risk factors for total number of deaths globally. In other words, **breathing polluted air ranks twice in the top 10 risk factors for death globally**. One report noted:

“Fine particle air pollution is the largest environmental risk factor worldwide, responsible for a substantially larger number of attributable deaths than other more well-known behavioral risk factors such as alcohol use, physical inactivity, or high sodium intake.”[110]

We are now living in a different environment compared to just 50 years ago. Take for example the ozone layer, which absorbs ultraviolet (UV) radiation from the sun. Damage to the ozone layer, from aerosol sprays that contain substances such as chlorofluorocarbons (CFS), has literally put holes in the protective ozone layer. That means we

are now dealing with an increase in UV radiation exposure compared to even 30 years ago[111]. That excess UV radiation means greater oxidative stress and DNA/protein damage in your body. What does this have to do with collagen? **A higher burden of oxidative stress leads to worse collagen health**[112], [113]. Thus, increasing your body's own natural resilience to oxidative stress and finding ways to reduce the increased oxidative stress from 21st century problems, such as air pollution, heavy metals, persistent organic pollutants, pesticides, herbicides, glyphosate, etc.,

will promote better collagen health[114], [115],[116],[117],[118].

Diabetes and Collagen Degeneration

Type 2 diabetics have a higher prevalence of Achilles tendon tears[119]. The risk of tendon ruptures seems to be increased in type 2 diabetic women but not men[120]. This could be because women have less total collagen, or due to a drop in estrogen that happens during menopause, which is a risk factor for osteoporosis - remember bones are made of collagen[121]. Interestingly, **estrogen replacement therapy enhances type I collagen synthesis** in skeletal muscle

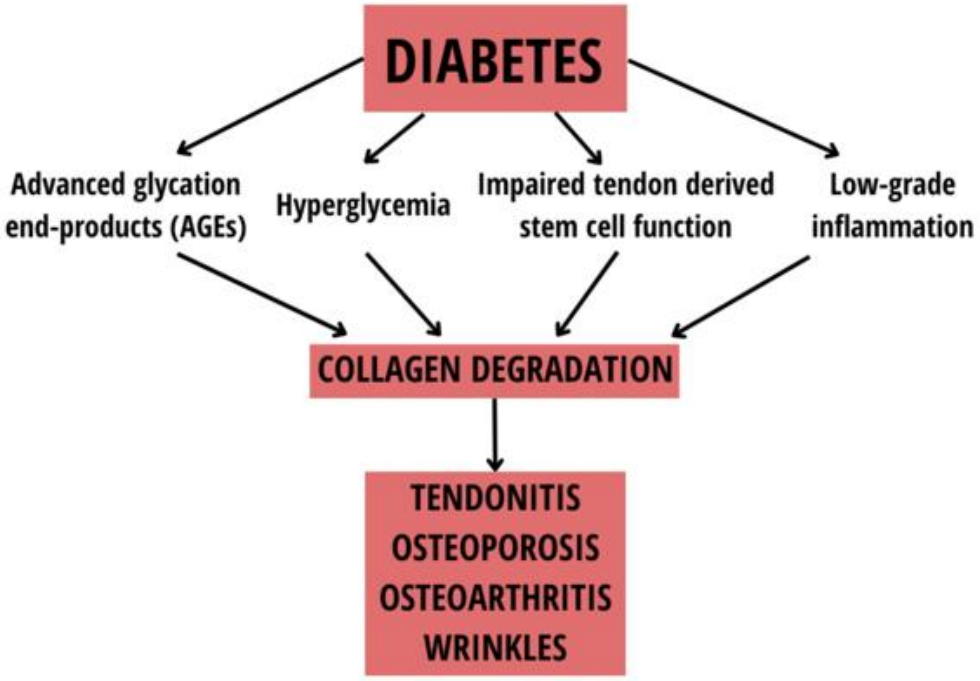
after acute exercise[122]. Even more worrisome, diabetes increases the risk of early menopause[123], which accelerates the loss of collagen in women. Similarly, **hypothyroidism increases the risk of tendon rupture[124] and osteoporosis[125]**. Ironically, **a low sodium diet increases the risk of hypothyroidism[126] and hypothyroidism can lead to sodium deficiency (as thyroid hormones help the kidneys retain sodium)[127]**. Persistent metabolic disorders that cause low-grade inflammation like obesity also wear down the tendons[128].

Collagen I gene expression decreases in tendon-derived stem cells when treated with high amount of glucose for 24-48 hours[129]. The high glucose environment can inhibit cell proliferation, induce cell apoptosis, and suppress tendon-related markers of tendon-derived stem cells (TDSCs) in vitro. Diabetics have impaired tendon derived stem cell function[130]. Thus, the population-wide increase in blood sugar levels is undoubtedly damaging collagen health.

Advanced glycation end-products (AGEs), which are molecules created between sugars and proteins reacting in the body, also contribute to diabetic

tendinopathy[131]. AGEs are also involved in the formation of wrinkles and skin aging as they break down collagen structures holding the skin firm[132],[133]. Glycation directly releases MMP-1 (matrix metalloproteinase-1), an enzyme that breaks down collagen[134],[135],[136]. Excess UV radiation from the sun also contributes to this by causing oxidative stress and increasing MMP-1 levels in the skin[137],[138]. **Glycated collagen accumulates in the skin and the cartilage as we age, and this accumulation dramatically increases after the age of 40[139].** Glycine is the perfect antidote for this, as it suppresses

AGEs, oxidative stress, supports collagen synthesis and lowers blood sugar levels[140],[141]. Supplementing GlyNAC (Glycine and N-acetylcysteine) at a dose of 100 mg/kg/day of both glycine and NAC lowers insulin resistance by 22% after just 14 days in type 2 diabetics[142]. Glycine also improves inflammation in the Achilles tendon[143]. Other supplements that can reduce AGE formation and improve collagen health include benfotiamine[144], a highly bioavailable form of thiamine, and beta-alanine[145], which increases carnosine levels in the body.



To prevent collagen and skin aging due to elevated blood glucose levels, you must live a lifestyle that maintains optimal blood sugar levels and insulin sensitivity. Regular physical activity and calorie restriction help to maintain better glycemic control and reduce AGE formation[146],[147]. Even just two weeks of inactivity reduces collagen protein

synthesis[148]. Of course, diabetes accelerates collagen degradation. However, it's been shown that maintaining tighter glycemic control can decrease glycated collagen formation by 25% in 4 months[149]. A low refined sugar diet will likely reduce the formation of AGEs in the skin[150],[151]. Overconsuming fructose or high-fructose corn syrup (HFCS) creates a lot of AGEs[152],[153],[154]. Consuming a diet low in AGEs for 4 weeks improves insulin sensitivity[155].

Here is a chart of the glycemic index (GI) of common foods[156]:

FOOD	Glycemic Index (GI) (glucose = 100)
HIGH-CARBOHYDRATE FOODS	
White wheat bread*	75 ± 2
Whole wheat/whole meal bread	74 ± 2
Specialty grain bread	53 ± 2
Unleavened wheat bread	70 ± 5
Wheat roti	62 ± 3
Chapatti	52 ± 4
Corn tortilla	46 ± 4
White rice, boiled*	73 ± 4

Brown rice, boiled	68 ± 4
Barley	28 ± 2
Sweet corn	52 ± 5
Spaghetti, white	49 ± 2
Spaghetti, whole meal	48 ± 5
Rice noodles†	53 ± 7
Udon noodles	55 ± 7
Couscous†	65 ± 4
BREAKFAST CEREALS	
Cornflakes	81 ± 6
Wheat flake biscuits	69 ± 2
Porridge, rolled oats	55 ± 2
Instant oat porridge	79 ± 3
Rice porridge/congee	78 ± 9

Millet porridge	67 ± 5
Muesli	57 ± 2
FRUIT AND FRUIT PRODUCTS	
Apple, raw†	36 ± 2
Orange, raw†	43 ± 3
Banana, raw†	51 ± 3
Pineapple, raw	59 ± 8
Mango, raw†	51 ± 5
Watermelon, raw	76 ± 4
Dates, raw	42 ± 4
Peaches, canned†	43 ± 5
Strawberry jam/jelly	49 ± 3
Apple juice	41 ± 2
Orange juice	50 ± 2
VEGETABLES	
Potato, boiled	78 ± 4

Potato, instant mash	87 ± 3
Potato, french fries	63 ± 5
Carrots, boiled	39 ± 4
Sweet potato, boiled	63 ± 6
Pumpkin, boiled	64 ± 7
Plantain/green banana	55 ± 6
Taro, boiled	53 ± 2
Vegetable soup	48 ± 5
DAIRY PRODUCTS AND ALTERNATIVES	
Milk, full fat	39 ± 3
Milk, skim	37 ± 4
Ice cream	51 ± 3
Yogurt, fruit	41 ± 2
Soy milk	34 ± 4
Rice milk	86 ± 7

LEGUMES	
Chickpeas	28 ± 9
Kidney beans	24 ± 4
Lentils	32 ± 5
Soya beans	16 ± 1
SNACK PRODUCTS	
Chocolate	40 ± 3
Popcorn	65 ± 5
Potato crisps	56 ± 3
Soft drink/soda	59 ± 3
Rice crackers/crisps	87 ± 2
SUGARS	
Fructose	15 ± 4
Sucrose	65 ± 4
Glucose	103 ± 3
Honey	61 ± 3

Interleukin-1 (IL-1) beta is a pro-inflammatory cytokine that is active in connective tissue, bone, and cartilage[157]. In human tendon cells, IL-1 beta increases MMPs, which destroy the collagen matrix. **Glutathione boosting supplements, such as NAC, alpha lipoic acid, and glycine, can suppress IL-1 beta signaling**[158]. NAC is also beneficial in reducing inflammation in the elderly[159].

Here are some nutraceuticals that can inhibit AGEs, MMPs and protect collagen[160],[161],[162],[163],[164],[165],[166],[167]:

- Glycine

- N-acetylcysteine
- Glutathione
- Berberine
- Carnosine
- Benfotiamine
- Beta-alanine
- L-carnitine
- Chromium picolinate
- Cinnamon
- Clove
- Alpha-lipoic acid
- Taurine
- Niacinamide
- Ginger
- Garlic
- Green tea (EGCG)
- Coffee
- Resveratrol
- Blueberries
- Pomegranate
- Hyaluronic acid

Certain drugs and medications can also harm collagen formation or increase its break down. They include oral glucocorticoids (like dexamethasone), inhaled glucocorticoids (like fluticasone) and corticosteroid injections[168],[169],[170],[171]. Fluoroquinolones, such as ciprofloxacin, a class of antibiotics, impair tendon healing and are linked to subsequent tendon ruptures[172],[173],[174]. **Statins** in animals **decrease the biomechanical strength of tendons, making them more susceptible to ruptures**[175].

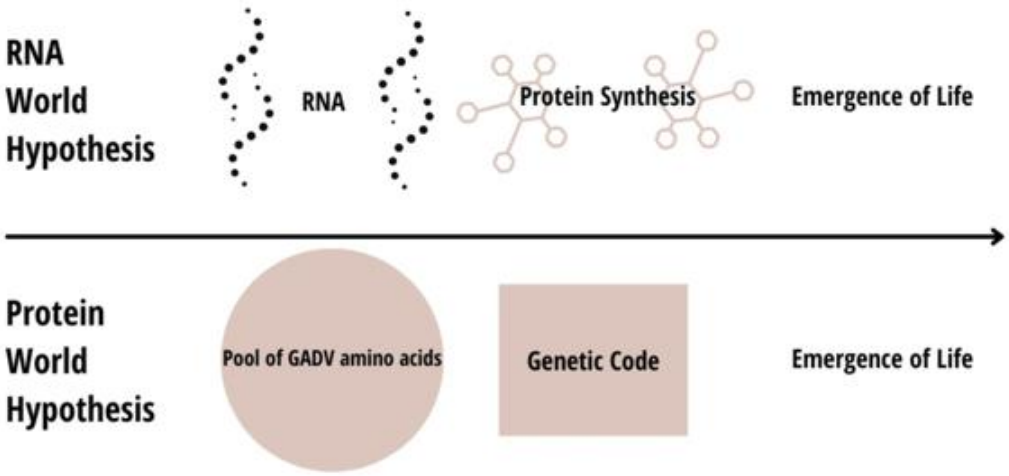
The main take-away from this chapter is that **numerous nutrients and**

supplements can help improve collagen health. Essentially, your collagen health is not only dependent on the amount of collagen or glycine you consume but also on many other factors including your nutrient status, glucose levels, and how much inflammation and oxidative stress is occurring in your body.

Chapter 2: Glycine and the Origin of life

Scientists have debated about the origins of life for decades. The two main debated theories are whether proteins (i.e., the ‘Protein World Hypothesis’) or RNA (i.e., the ‘RNA World Hypothesis’) came first[176]. In 1989, the Nobel Prize was awarded to Altman and Cech suggesting that RNA molecules preceded proteins since they could carry genetic information and take part in catalytic activities as well as structural integrity[177]. However, more recent

studies have challenged the theory that RNA molecules came first arguing that ancient peptide catalysts lead to the formation of the genetic code[178]. **Currently, the Protein World Hypothesis, also known as the GADV-protein world hypothesis, is the most accepted theory considering that the early conditions of Earth would have formed amino acids and peptides**[179]. GADV stands for glycine (G), alanine (A), aspartic acid (D) and valine (V)[180].



Regardless of which theory is correct, all scientists agree on the crucial role that amino acids play in the body as they are literally the building blocks of proteins. You may have heard of enzymes, which are involved in over 5,000 vital reactions in the body[181]. Well, those enzymes are protein molecules. Proteins also help to give cells their structural integrity[182]. Considering that proteins are the catalyst for biochemical reactions, they are

considered the '*workhorses*' of the cell[183]. In other words, if you want enzymes and chemical reactions to occur in the body you must have proteins to do that.

For the *'Protein World Hypothesis'* to be correct, then peptides, or compounds containing two or more amino acids linked in a chain, would need to have formed during the early conditions on Earth. The problem, however, was finding a catalyst surface that could form peptides during this time. Eventually, it was discovered that **minerals were capable of being catalysts that could form peptides on**

our young planet[184]. In other words, minerals would have allowed amino acids to interact with each other forming polymers. Collagen is an example of a polymer, as it is composed of three identical amino acid chains. What this suggests is that **the earliest '*collagen-like*' substance would have formed through the interaction between minerals and ancient amino acids such as glycine and alanine.** The authors of a recent review paper summarized this idea nicely in the following:

> *"The presence of these minerals is so wide that a variety of places on Earth*

render them a vital crystalline structure upon which the sorption and oligomerization of amino acids might have taken place on early Earth, some 4 billion years ago. This would give some credence to the protein first hypothesis as opposed to the RNA first one; in that it has been shown that it is possible to synthesize oligomers (chains of amino acids, our insertion).”[185]

Out From the Salty Ocean: Proteins, Not RNA, Would Have Existed

"*The idea that a very early stage of life was the "RNA world" encounters crucial problems concerning the formation of its building blocks and their stability in a prebiotic environment. Instead, it seems much more likely that a "peptide world" originated first and that RNA and DNA took up their part at a much later stage. It is shown that amino acids and peptides can be easily formed in a realistic primordial scenario and that these biomolecules can start chemical evolution without the help of RNA. The*

origin of biohomochirality seems strongly related to the most probable formation of the first peptides via the salt-induced peptide formation (SIPF) reaction"[186]. ~ Daniel Fitz et al. 2007.

The idea that life formed in the ocean is currently the most accepted by scientists today, as the UV radiation from the sun was too intense prior to the formation of the ozone layer for anything to live on the surface of the Earth. In other words, **proteins were likely formed prior to RNA on primordial Earth as RNA would not have been able to survive in the salty ocean and would have been destroyed within minutes**[187].

Peptides and proteins however are stable, even under salty conditions, furthermore they possess all the needed properties to build simple life forms. Thus, the starting point of life on Earth began with proteins not RNA. *“Around 4 billion years ago, the bombardment of the earth declined, and permanent, still rather hot oceans could form, being the most likely places where a chemical evolution could start to form a first form of life.”*[188]

When Earth was first formed 4.5 billion years ago it was a hot and hostile place. At this time the Earth was being pounded by meteors and asteroids for several

hundred million years. However, it was the presence of liquid water that is thought to be the essential prerequisite for life. Evidence suggests that as early as 4.4 billion years ago there were oceans on the Earth's surface[189],[190]. These oceans were likely evaporating as quickly as they were forming due to large meteor impacts that were occurring on early Earth. However, around 4 billion years ago the bombardments of Earth declined with more permanent, hot oceans forming. To give you an idea of just how hot these oceans were, it has been estimated that their temperatures ranged anywhere from 70 to 100°C or 158-212°F (that's 1.5 to 2 times hotter

than a hot tub!). These scalding hot oceans would have contained numerous dissolved minerals such as sodium, potassium, magnesium, and calcium and were very acidic due to the high carbon dioxide concentration in the atmosphere[191]. To sum it up, early Earth was a hot, salty pool of minerals and amino acids, but which amino acids? And where did they come from?

The earliest evidence for life on Earth dates back as far as 3.5-3.8 billion years ago based on fossilized cyanobacteria, or blue-green algae such as spirulina, discovered near Western Australia and South Africa[192],[193]. We must thank

these photosynthetic bacteria for the increased oxygen levels in our atmosphere that lead to the development of the ozone layer, which was necessary for blocking out sunlight radiation so that life could exist on the surface of our planet. **Cyanobacteria can grow in very salty environments because they can synthesize something called glycine betaine (GB)[194].** Glycine betaine is also produced by plants so that they can tolerate high salt environments[195]. Increasing the glycine betaine content of plants and algae is now being investigated to support their growth during conditions that would

either reduce their yield or completely prevent them from growing at all[196]. Other bacteria use choline to make glycine betaine, but plants and cyanobacteria can endogenously synthesize glycine, which is then methylated in 3 steps to glycine betaine[197]. Mammals have glycine receptors in their bodies to prevent them from dying when blood sodium levels go too low[198]. Additionally, our mitochondria would not be able to recognize proteins, nor would our mitochondria function properly, without glycine[199]. What all of this means is that **the largest biomass and the very first**

lifeform on Earth (e.g. blue green algae) would not have been able to exist in the oceans without glycine. At the very least, it suggests that glycine has been around for a minimum of 3.5 billion years[200]. But how would cyanobacteria form? The answer may be glycine again.

From Space and Comets: Glycine's Arrival on Earth

Imagine a substance that could spontaneously form in space. Now imagine that this substance could be made from comet ice hitting the Earth. This substance would have been around since the dawn of time and the very beginning of life on Earth. This substance is known as glycine, which is the smallest amino acid[201]. Glycine's presence in space was confirmed in 2009 by NASA who analyzed samples from the comet Wild 2[202]. In 1970, glycine had already been previously identified in the Murchinson

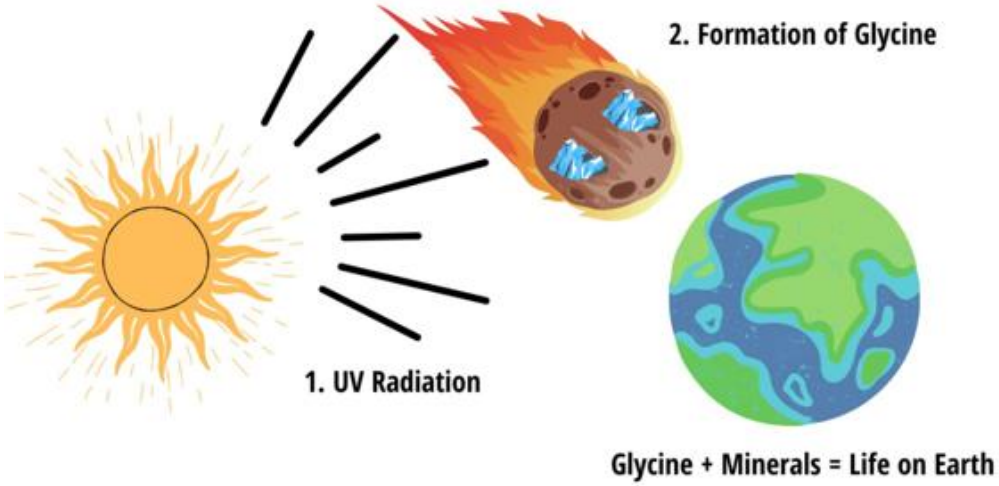
meteorite[203]. It's been debated whether there's glycine outside of the Solar System[204] and spectral lines of a glycine precursor called aminoacetonitrile have been discovered in the Large Molecule Heimat, which is a giant gas cloud in the Sagittarius constellation near the galactic center[205].

To replicate how organic matter is formed in deep space, Briggs and colleagues, using a chemical reaction called photolysis, took mixtures of ammonia, carbon monoxide and water and yielded several substances, but the only amino acid that formed was glycine[206],[207]. **When meteorite ice is irradiated with**

UV light, glycine, alanine, and serine are formed. The compression of comet ice on early Earth also could have formed glycine[208].

Even more promising are the Miller-Urey experiments which were conducted in the 1950s, wherein they generated glycine using water, molecular hydrogen, methane, and ammonia, which are all substances that were available on early Earth[209]. The point is that **glycine was likely one of the first, if not the first, amino acid in the early Earth's atmosphere, as well as being formed in hydrothermal vents and from meteors impacting Earth.** Even

chemical analysis of the type of rocks on Mars has found them to contain glycine[210]. To summarize all of this in one sentence: *"**Glycine may be an ancient molecule involved in the evolution of life on Earth some 3.8 billion years ago**."* [211] That's a profound statement. And it's backed by a lot of research, scientific experiments, and data. But why does any of this matter? Well, if glycine was one of the very few substances available on early Earth, that would mean that life itself would have evolved with glycine being one of the most, if not the most important, building block.



Considering that **glycine is the smallest and most simple amino acid, it is literally the smallest building block of life**. Furthermore, the system that metabolizes glycine in the body, called the glycine cleavage system, is found in bacteria, plants, and animals[212], suggesting that **glycine** has been around since the beginning of life itself and **may be the most crucial substance for all life on Earth, including us!** It has even

been suggested that **glycine was the first amino acid to be incorporated into the genetic code**, followed thereafter by serine, aspartic and/or glutamic acid[213]. In fact, the original genetic code is said to have coded for only five amino acids glycine, aspartate, glutamate, alanine, and valine[214],[215],[216],[217].

What all of this means is that our health may hinge on getting an optimal amount of glycine and collagen in our diet. In the following chapters you will get to know this amino acid a little bit better to understand its effects on our health.

To summarize

)Glycine was said to be the first amino acid on Earth some 3.8 billion years ago

)Glycine is the smallest and simplest amino acid and literally a ‘building block’ of life

)The system that metabolizes glycine is found in bacteria, plants, and mammals (including humans)

)Glycine is the most abundant amino acid in collagen, making up one out of every third amino acid

Chapter 3: The Short and Sweet on Glycine

Glycine was one of the first amino acids ever to be discovered and the first to be isolated from a protein. In 1820, the French chemist Henri Braconnot obtained glycine from acid hydrolysis of gelatin[218]. He initially called it *“sugar of gelatin”* because of its sweet taste[219]. However, another French chemist Jean-Baptiste Boussingault revealed that it contained nitrogen, making it an amino acid not a sugar[220]. In 1848, a Swedish chemist proposed the name glycine,

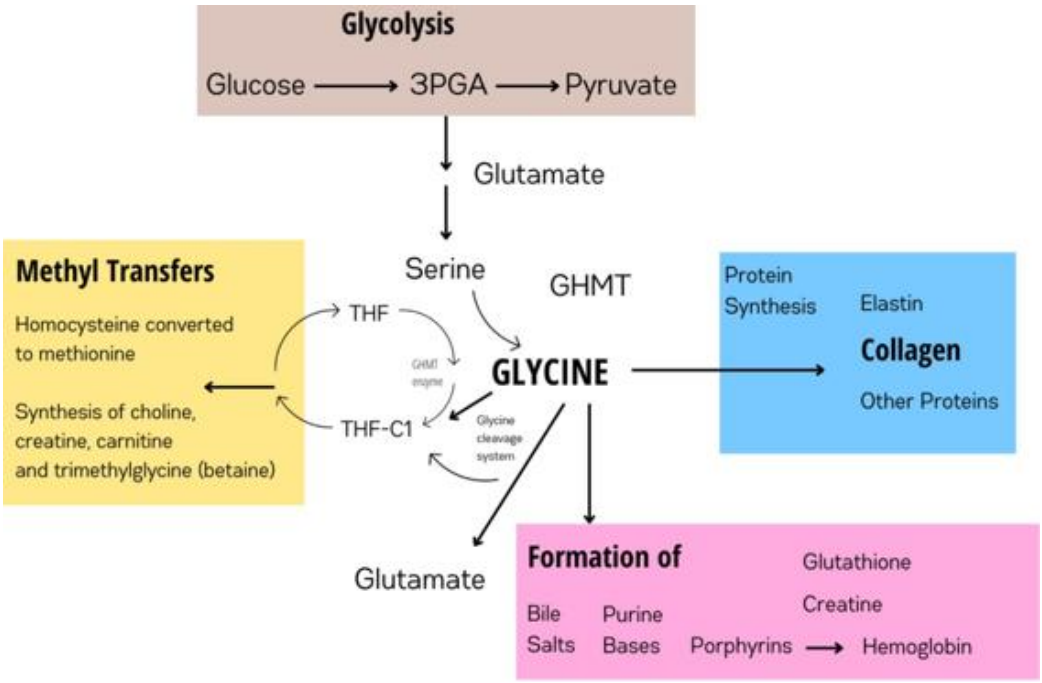
which is derived from Greek word γλυκύς or *"sweet tasting"*[221],[222].

Glycine is the smallest of the 20 amino acids and it also has the smallest side chain composed of a single hydrogen atom. Glycine is considered a non-essential amino acid because the body can synthesize it. However, as you will soon learn, the body does not make nearly enough glycine to support *optimal* collagen turnover[223],[224]. This means that glycine is a 'conditionally essential' amino acid. If you want optimal collagen health, then you need to supplement with glycine. This is because the amount of

glycine you get from a typical diet and endogenous synthesis is not enough.

The reason why we don't make optimal amounts of glycine is because glycine synthesis in the body is not regulated by its demand. There is a 'weak link in metabolism' when it comes to glycine biosynthesis[225]. The synthesis of glycine depends on the enzyme glycine hydroxymethyltransferase (GHMT) and the need for adding one carbon group (C_1) to tetrahydrofolate (THF-C_1). This is because GHMT produces glycine and THF-C_1 in equimolar amounts with no independent regulation based on glycine

need. Thus, the amount of glycine is determined by the need for C_1 units on tetrahydrofolate (THF). Moreover, there is no downstream mechanism to make more glycine from the glycine cleavage system as it is thermodynamically irreversible, where glycine is broken down into C_1, carbon dioxide and ammonia[226].



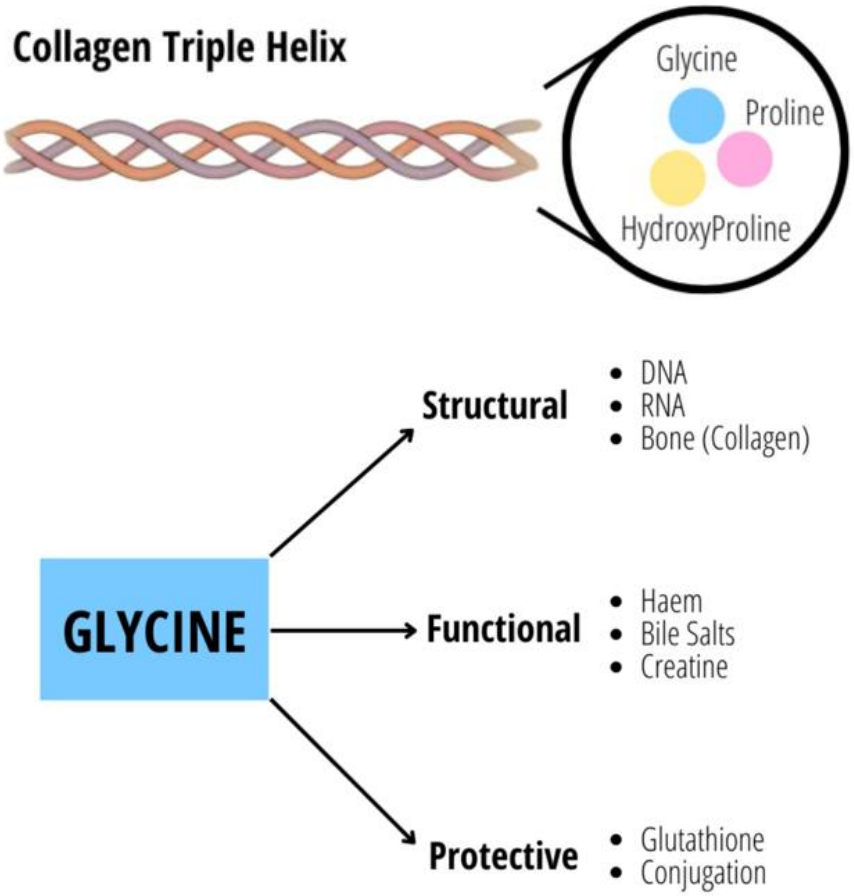
The synthesis of glycine from serine and the use of glycine for different metabolic functions (Adapted From: Melendez-Hevia et al 2008)

The reason why natural selection has not found a solution to the glycine constraint is because a suboptimal glycine status does not affect survival and reproduction, but it does reduce quality of life in old age (think osteoarthritis and osteoporosis for example). This makes glycine *'conditionally essential'* as the ability for us to synthesize it has a fixed limit. In the words of Christensen (1982), *"the fact that a given amino acid can be synthesized in metabolism does not mean it is enough to sustain all metabolic*

needs.”[227] Insufficient glycine isn’t life-threatening but chronic deprivation may cause what’s called a glycine deficiency syndrome, reducing the overall quality of life and increases the risk of numerous chronic diseases.

Glycine and Collagen

Glycine makes up every third amino acid in collagen, which is why there is such a large requirement of glycine for optimal collagen turnover. The reason why **glycine** makes up every third amino acid of collagen is because **it is the only amino acid small enough to pack into the central core of the triple helix**, allowing the three polypeptide chains to come close enough to wind together tightly[228]. **Glycine also helps to form DNA, RNA, elastin,** and other proteins, such as **glutathione** (antioxidant), **creatine** (energy), **porphyrin rings** (heme), and **bile salts**[229],[230],[231],[232].



Adapted From: Jackson (1990)[233]

The less collagen or glycine you consume the slower your collagen turnover[234]. A slow collagen turnover increases the damage that occurs to your collagen, such as glycation and oxidation and reduces collagen

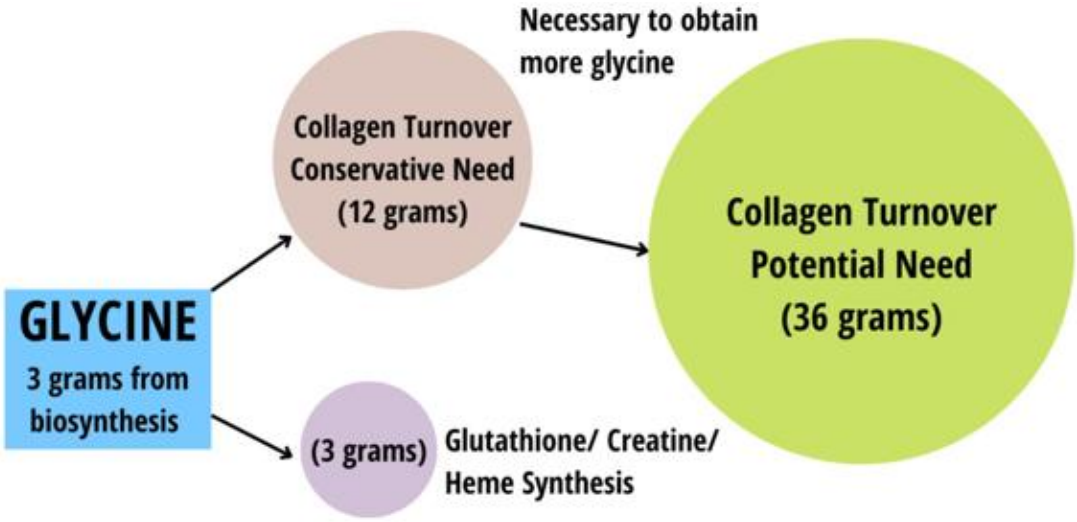
deposition into tissues[235]. Up until very recently, it was thought that collagen turnover was very slow with a lifespan of several years. However, recently it has been shown that collagen turnover is a significant proportion of the entire daily protein turnover.

In a seminal paper published by Enrique Melendez-Hevia and colleagues in 2009, **it was discovered that the need for glycine for optimal health is around 15 grams per day (at least 12 grams per day for optimal collagen turnover plus another 3 grams for the formation of things like glutathione, creatine, heme, etc.)[236]. Considering that we**

only make around 3 grams of glycine per day, and only consume around 2-3 grams of glycine per day, that means that almost all of us are in a 10-gram glycine 'deficit' each day. To be clear, this is an estimate, and it assumes a 95% recycle rate of glycine during collagen turnover with only 5% being lost in the body. However, if glycine's recycle rate is more like cysteine, then glycine would only have an 85% recycle rate. If that is the case, as currently we aren't exactly sure what glycine's recycle rate is, then we could need three times more glycine - not 12 grams but 36 grams for optimal collagen health.

Glycine biosynthesis is also lower on diets low in certain nutrients, such as vitamin B12 and vitamin C[237]. Thus, **there is a high probability that most people have a glycine status that is suboptimal, needing anywhere from 10 to 36 grams of supplemental glycine per day to support optimal collagen turnover.** Regardless of what the exact amount of glycine is for optimal collagen health, as you will soon discover in later chapters, there are clear benefits when supplementing with 10-20 grams of glycine per day. Moreover, the amount of glycine that would be needed to be toxic in a human has been estimated to be 600 grams per day

based on animal studies (human studies have safely given up to 80 grams of glycine per day in schizophrenic patients) [238].


Necessary to obtain more glycine
Collagen Turnover Conservative Need (12 grams)
Collagen Turnover Potential Need (36 grams)
GLYCINE
3 grams from biosynthesis
(3 grams)
Glutathione/ Creatine/ Heme Synthesis

In 1981, Neuberger suggested that the requirement for glycine synthesis was 10-50 times higher than its dietary intake[239]. Gersovitz and Yu in 1980 and 1985, respectively, showed that **glycine synthesis is inadequate to meet**

metabolic demands in adults on either a low protein diet or a diet low in non-essential amino acids. Alan A. Jackson from the Department of Human Nutrition, University of Southampton, United Kingdom wrote that only the amino acids alanine, aspartate and glutamic acid should be considered truly 'non-essential' as their carbon skeleton is readily available from intermediary metabolism and readily undergoes transamination reactions. Thus, **glycine should potentially be considered an essential amino acid but certainly a 'conditionally essential' amino acid.**

The Need for Glycine [Adapted From: Melendez-Hevia et al (2008)]

Process	**Glycine**
Synthesis in the body	3 g/day
Intake	1.5 to 3 g/day
Requirement for metabolites	- 1.5 g/day
Requirement for optimal collagen turnover	- 12 g/day
Requirement for other proteins	- 1g/day
Balance	**-8.5 to -10g/day**

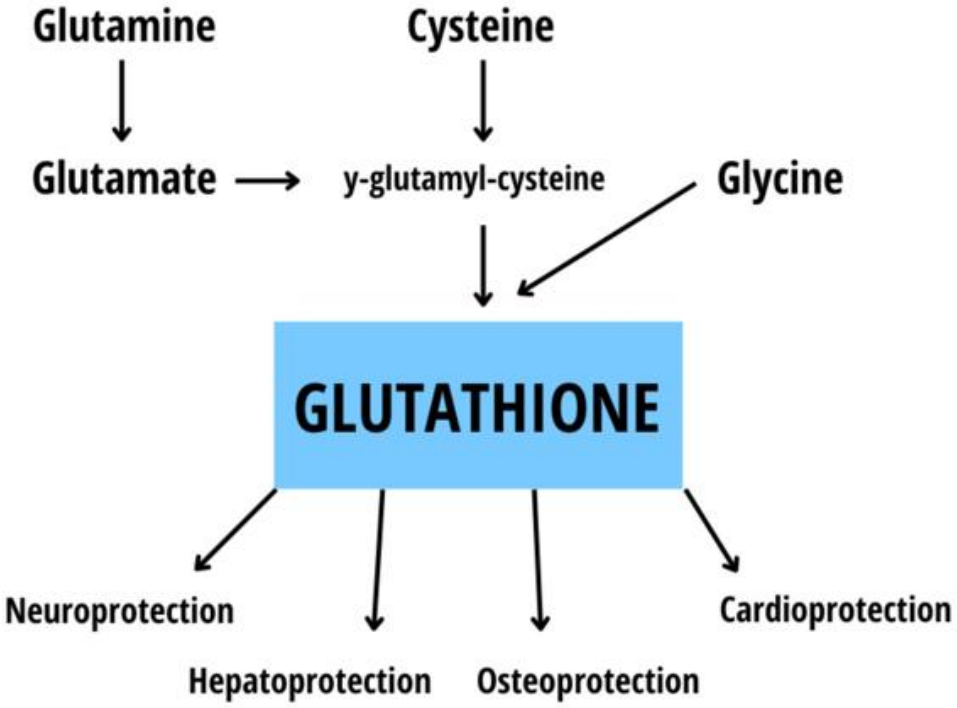
The problem with a suboptimal glycine intake appears to be real and does not just apply to humans but to all animals that are over 40 kg because collagen

problems, such as osteoarthritis, is well documented in other species, including coyotes, dogs, chimpanzees, gorillas, giraffes, rhinoceros, and elephants[240], [241],[242],[243]. Skeletons of large dinosaurs from the Jurassic (100-150 million years ago) have also shown evidence of osteoarthritis[244],[245].

Glycine and Glutathione

Glutathione is the body's master antioxidant that has many protective and anti-inflammatory effects in the body. The primary role of glutathione is to protect cells against oxidative stress, reactive oxygen species and heavy metals[246], [247]. **Deficient glutathione synthesis underlies the increased oxidative stress in aging, contributing to age-related diseases like neurodegeneration, heart disease, liver disease and cancer, and can be fixed with dietary cysteine and glycine supplementation**[248],[249]. Glutamine and cysteine are needed for glutathione

synthesis, but glycine is needed as well[250]. That's because glycine, glutamine and cysteine make up glutathione[251]. **Additionally, glutathione synthesis is rate-limited by glycine[252].**



Adapted From: Lu (2013) and Franco et al (2007)[253],[254]

Taking cysteine precursors, in the form on N-acetylcysteine (NAC), can increase glutathione levels[255],[256]. However, glycine can be another potent one. **Supplementing glycine boosts glutathione and reduces oxidative stress in humans**[257]. Besides higher glutathione levels, glycine also helps to combat reactive oxygen species by inhibiting NADPH oxidase (NOX), which is the main source of superoxide radicals in the body, thereby raising NADPH levels and lowering oxidative stress[258], [259]. NOX is involved in inflammation and oxidative stress[260],[261]. **In patients with metabolic syndrome, 15 grams of**

glycine per day in 3 divided doses (5 grams three times daily) **reduces oxidative stress and improves systolic blood pressure**[262].

Glutathione reduces the formation of Advanced-Glycation End-Products (AGEs) that cause glycation, and acceleration of wrinkles and AGEs wreak more havoc when glutathione levels are low[263],[264]. **Glycine suppresses the AGE pathway,** as it reduces the formation of AGEs and increases the breakdown of precursors to AGEs, such as methylglyoxal, thereby reducing oxidative stress[265],[266]. **In diabetics, supplementing with 5 grams of**

glycine 3-4 times a day improves A1C levels[267],[268]. Glycine also counteracts complications in diabetes[269]. Glycine supplementation improves insulin sensitivity in humans and helps lower blood glucose levels by potentiating the effects of insulin[270],[271]. Thus, **one of the best anti-aging strategies is to ensure an adequate glycine intake.**

A 2019 paper by Dr. James DiNicolantonio notes:

> *"Supplemental glycine may be useful for the prevention and control of atherosclerosis, heart failure, angiogenesis associated with cancer or retinal disorders and a range of*

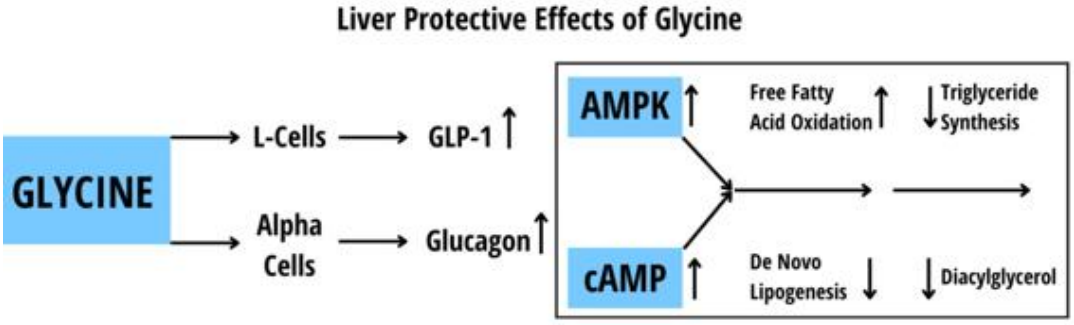
inflammation-driven syndromes, including metabolic syndrome."[272]

Patients with severe inflammatory conditions have been shown to have elevated urinary 5-L-oxoproline levels, which is thought to reflect low glycine status, with the sickest individuals and those who died having the highest concentrations of 5-L-oxoproline in the urine[273],[274]. The elevated urinary levels of 5-L-oxoproline improved when their condition improved. This suggests that health conditions can reduce glycine status, whereas improving health conditions improves glycine status. **Glycine supplementation can**

decrease pro-inflammatory cytokines and increase immunomodulatory interferon-gamma[275],[276]. Acute phase **inflammatory proteins,** such as C-reactive protein, are rich in glycine, and they **create a bigger drain on the limited glycine pool.** This suggests that glycine deficiency may lead to or contribute to the morbidity and mortality of inflammatory conditions.

Glutathione is synthesized in the liver – the central organ of detoxification and energy homeostasis[277]. Knockout mice without liver glutathione synthesis die within a month of birth[278],[279]. Thus, your liver health and ability to produce

glutathione is quite important, especially for managing oxidative stress and aging. **Glycine can counteract many of the harmful effects that excess sugar intake has on the liver, adiposity, and vascular function in rats**[280],[281]. Glycine also counteracts the harmful effects of fructose on the liver by stimulating glucagon-like peptide 1 (GLP-1) and glucagon, which then helps to prevent liver fat storage through the AMPK and cAMP pathways[282].



Adapted From: DiNicolantonio and McCarty (2014)[283]

Glycine has an important role in excitatory and inhibitory neurotransmitters as well via N-methyl-D-aspartate type glutamate receptors and glycine receptors[284]. Glycine is also great for improving sleep. Taking **glycine before bed can improve sleep quality as it lowers body temperature, accelerating sleep efficiency**[285]. Glycine supplementation increases serotonin, which is needed for producing the sleep hormone melatonin[286],[287]. **People who ingested 3 grams of glycine within 1**

hour before bedtime saw an improvement in subjective sleep quality, fell asleep faster, and were less sleepy during the day[288].

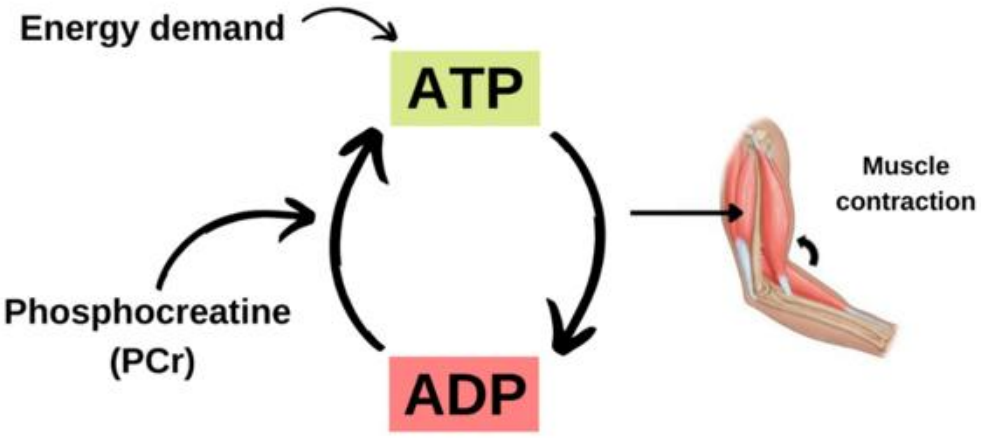
Glycine and Creatine

For exercise performance, creatine is one of the most research-backed and effective supplements[289]. It promotes muscle hypertrophy, strength, power and reduces the incidence of injuries[290],[291],[292],[293],[294]. Supplementing with creatine monohydrate increases maximal strength and power by 5-15% in the short term[295]. There is a correlation between an increase in skeletal muscle creatine stores and performance benefits[296],[297].

Creatine is synthesized in the liver and pancreas from the amino acids arginine, glycine and methionine[298],

[299],[300]. In glycine-deficient animals, muscle creatine content is low[301]. That's a big deal because 95% of your total creatine stores are in skeletal muscle[302]. About 2/3rds of that is in the form of phosphocreatine (PCr), also known as creatine phosphate (CP), and the rest exists as free creatine. Reshuffling ADP back into ATP during exercise is greatly dependent on the amount of muscle PCr levels (this is because it is a source of phosphate, needed to convert ADP to ATP)[303],[304]. Supplementing creatine increases the amount of phosphocreatine[305],[306],[307].

However, **glycine can also raise creatine levels**[308],[309].



Source: DiNicolantonio, Land & Kennedy (2021) 'WIN'

Trimethylglycine (TMG), also known as betaine, increases the biosynthesis of creatine[310]. **Taking 2.5-5 grams of betaine a day, divided into two doses, has been shown to help fat loss and subjective markers of fatigue during exercise**[311],[312],[313]. However, the total

performance enhancing effects of betaine, or glycine for that matter, are still significantly lower than creatine[314]. Thus, although glycine is a contributor to creatine synthesis, it's still important to take creatine. You can get creatine from meat and fish but reaching an optimal dose of 3-5 grams a day would be quite difficult through diet (necessitating around 1.5-2.5 pounds of red meat per day, respectively). Thus, creatine supplementation is the fastest and easiest way to top off your creatine stores.

Glycine and Methionine Restriction

One of the more interesting aspects of glycine is its positive impact on longevity and lifespan in other species. A diet consisting of 8% glycine has been found to extend the lifespan of mice (2% in females and 6% in males)[315]. **In rats, glycine supplementation leads to a lifespan extension of 30-40%[316]**. Glycine also extends the lifespan of fruit flies and nematodes[317]. **Adding glycine** to fibroblasts from 97-year-old people **restored their mitochondrial function to much younger levels**[318].

In other words, glycine may have life extending and age reversing properties.

The primary mechanism by which glycine has life extension effects is by mimicking methionine restriction[319]. **Methionine restriction (MR) increases lifespan and slows down aging in animal models[320]**. MR is also a potential strategy in the treatment of cancer as cancer cells need methionine to survive[321]. Excess methionine raises homocysteine, which is associated with aging and cardiovascular disease[322], [323]. **Glycine prevents the negative effects of methionine overload, such as reducing elevated homocysteine**

after high protein meals and reducing excess S-adenosylmethionine, which is implicated in elevated blood lipids, fatty liver and heart disease[324],[325],[326],[327],[328],[329]. Trimethylglycine (TMG) and choline can also lower circulating homocysteine[330].

Methionine is the most abundant proteinogenic essential amino acid in the human diet[331],[332]. Methionine's role is to donate methyl groups and regulate gene expression that support growth pathways in the body, such as initiating protein synthesis and growing new blood vessels[333]. It cannot be synthesized and thus must be obtained from dietary

sources. Animal proteins are the most abundant sources of methionine, whereas plant-based proteins are much lower[334]. This could be part of the reason why plant-based foods are associated with aspects of longevity. A 2020 BMJ meta-analysis of 32 prospective cohort studies found that **for every 3% increase in daily consumption of plant protein the risk of death decreased by 5%[335].** There are probably many variables that contribute to that, such as the intake of processed animal foods and other harmful things that are commonly consumed with animal foods (burger and

fries, for example), but the lower methionine content of plant-based foods may contribute as well. Regardless, **we believe that consuming an animal-based diet composed mainly of 100% grass-fed meat/organs, pastured eggs and fermented dairy is optimal for health and longevity, if it is balanced with adequate amounts of glycine and alkalinity** (alkaline supplements such as sodium citrate/bicarbonate or fruits and vegetables)[336],[337].

The increased lifespan seen in methionine restriction is thought to be caused by the decrease of IGF-1 (Insulin-Like Growth Factor 1) and

mTOR (Mammalian Target of Rapamycin)[338]. Leucine, another essential amino acid, is the main activator of mTORC1[339]. Reduced mTOR activity increases lifespan in different yeast species, bacteria, and mice[340],[341],[342]. Higher mTOR inhibits autophagy, which promotes tumorigenesis, diabetes, cell senescence and aging[343]. Dysregulated mTOR activity is also seen in the brain of Alzheimer's patients[344],[345].

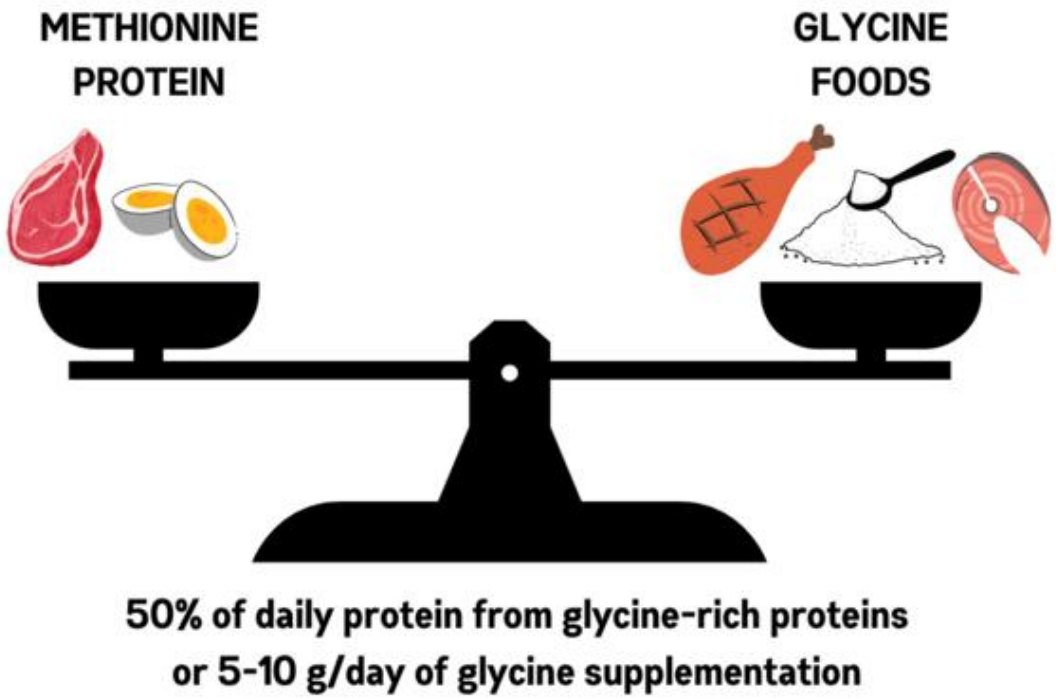
Methionine restriction is very difficult and impractical as methionine is found in almost all foods. Low methionine intake can also promote sarcopenia and slow

down detoxification pathways[346]. Methionine is also essential for reversing damaged methylation receptors caused by chronic stress[347]. **Fortunately, glycine supplementation can yield the same benefits of methionine restriction without restricting methionine[348].** You just need to balance your methionine intake with glycine. **Methionine depletes glycine levels and for every gram of methionine consumed your demand for glycine increases by 0.5-1 grams[349].**

A general rule is to consume an equal amount of protein in methionine-rich

protein and glycine-rich protein and/or take a glycine supplement. Muscle meat is higher in methionine, whereas glycine is found more in organ meats, tendons, ligaments, drumsticks, turkey necks and other collagenous meats. Plants do provide 3-4 times more glycine than methionine, but they contain low absolute amounts of glycine (don't expect to get your glycine needs from plants). Collagen, such as skin, bones, and connective tissue, provides 25 times as much glycine as methionine. Moreover, collagen is a good source of glycine. That's why it's recommended to include collagen-rich foods (or take collagen supplements) in addition to

consuming muscle meat. Taking an additional glycine supplement in doses of up to 10 grams a day is also likely to be beneficial.



Here is an overview of the highest methionine foods[350]:

- **Dried Egg Whites**: 2.8 grams per 3.5 ounces (100 grams)

- **Dried Spirulina**: 1.2 grams per 3.5 ounces (100 grams)
- **Lean Beef**: 1.1 grams per 3.5 ounces (100 grams)
- **Brazil Nuts**: 1.1 grams per 3.5 ounces (100 grams)
- **Lean Lamb**: 1.1 grams per 3.5 ounces (100 grams)
- **Bacon**: 1.1 grams per 3.5 ounces (100 grams)
- **Parmesan Cheese**: 1.0 gram per 3.5 ounces (100 grams)
- **Chicken Breast**: 0.9 grams per 3.5 ounces (100 grams)
- **Tuna**: 0.9 grams per 3.5 ounces (100 grams)

Here is an overview of the highest glycine foods[351]:

- **Dry Gelatin Powder**: 19.1 grams per 3.5 ounces (100 grams)
- **Pork Skin Snacks**: 11.9 grams per 3.5 ounces (100 grams)
- **Low-Fat Sesame Flour**: 3.4 grams per 3.5 ounces (100 grams)
- **Chicken Skin**: 3.3 grams per 3.5 ounces (100 grams)
- **Dried Egg Whites**: 2.8 grams per 3.5 ounces (100 grams)
- **Bacon**: 2.6 grams per 3.5 ounces (100 grams)
- **Lean Beef**: 2.2 grams per 3.5 ounces (100 grams)
- **Cuttlefish**: 2.0 grams per 3.5 ounces (100 grams)
- **Lean Lamb**: 1.8 grams per 3.5 ounces (100 grams)

You don’t need to go on a low methionine diet for longevity (in fact, that would likely have the opposite effect). However, you should incorporate more glycine-rich proteins to “*balance out*“ the methionine. It’s not natural for our bodies to only eat muscle meat all the time either. In the past, people would eat the entire animal from “*nose to tail*“.

Absorption and Excretion of Glycine

Glycine is easily absorbed through the gastrointestinal tract. After the ingestion of glycine (1 g/10 lb. of bodyweight) normal human subjects show an acute rise in plasma glycine levels, peaking in 60-90 minutes[352]. Gelatin, in fairly large amounts (100g or 3.5 oz.), can also raise glycine concentrations 10x higher than normal within an hour of consumption[353]. Dispersion of glycine into the brain and cerebrospinal fluid is rather slow[354]. Muscle cells aren't very permeable to glycine, but liver and

kidney cells are[355]. **Patients with liver cirrhosis, celiac disease, ulcerative colitis, or pernicious anemia have abnormal glycine absorption and glycine deficiency**[356],[357]. Glycine is involved in heme biosynthesis and can promote hemoglobin output[358],[359]. Vitamin C deficiency also leads to decreased glycine in skeletal muscle[360].

Glycine is depleted by benzoic acid as it is conjugated with it to form hippuric acid and excreted by the kidneys[361]. Benzoic acid can be used to preserve foods, such as fruit juices, soft drinks, salad dressings, and sauces. It inhibits the growth of mold, bacteria and yeast

and has been used for up to 100 years[362]. Many processed foods contain benzoic acid. Some natural foods and compounds like cinnamon and cranberries also have some benzoic acid[363]. You can also find benzoic acid in cosmetics, mouthwash, shampoo, sunscreen, and toothpaste[364]. According to the WHO, **benzoic acid** isn't carcinogenic, but it **could be depleting your glycine stores**.

Benzoic acid found in sodas, iced tea and lemonade lead to glycine loss out in the urine as hippuric acid. Additionally, **the chlorogenic acid from coffee can form benzoic acid and deplete**

glycine. Light roasted coffee has more chlorogenic acid with up to 200 mg per serving with about 50% of it forming benzoic acid[365]. Thus, 1 shot of espresso may deplete 50 mg of glycine. **A 7 oz. cup of coffee** containing 70-350mg of chlorogenic acid and creating 35-200 mg of benzoic acid, **depletes up to 100 mg of glycine**[366],[367]. **The average American consumes 4 cups of coffee per day, which makes them lose up to 400 mg of glycine a day** as hippuric acid in the urine. This could certainly add up over time creating a large glycine deficit in the body. Combine that with 1 liter of any combination of

soda, iced tea or lemonade and you could lose an additional 100 mg of glycine. Add in another 100 mg loss from 6 oz. of emulsified sauces and dressings, 100 mg additional loss from 6 oz. of a prepared salad and 25-50 mg loss from 3 oz. of mayonnaise[368]. Those numbers add up fast. **In total, the average American could be losing up to 625-1,050 mg of glycine from daily beverages and foods**, which doesn't include toothpaste, deodorant, facial cleansers, cinnamon, cranberries, pickles, and plums[369].

- Coffee – (4-8 cups of coffee) – Up to 400-800 mg glycine loss

- Soda/Iced tea/Lemonade/Fruit juice (1 liter) - 100 mg glycine loss
- Sauces/dressings (6 oz.) – 100 mg glycine loss
- Mayonnaise (3 oz.) – 25-50 mg glycine loss
- Total loss: 625-1,050 mg of glycine/day
    - This doesn't include losses from toothpaste, deodorant, facial cleansers, cinnamon, cranberries, pickles, and plums

Methionine depletes glycine and every gram of methionine consumed increases our glycine need by around 0.5-1 gram of glycine. Excess methionine and leucine

intake also reduces the bioavailability of glycine by up to 90%. Even if the reduction is just 50% less absorption of glycine that is a very large decrease in glycine bioavailability. Thus, if you're eating only 3 grams of glycine from food but only absorbing 1-1.5 grams, and are also losing 1-1.5 grams to benzoic acid in the diet, then you're solely relying on the limited amount of glycine your body can synthesize naturally, which is only about 3 grams per day. This would leave zero glycine left over to help with optimal collagen turn over.

Substances that deplete glycine:

Consuming or absorbing benzoic acid or benzoic acid forming substances (chlorogenic acid)

- Green tea extract
- Light-roast coffee especially (but also dark-roast coffee)
- Processed foods containing benzoic acid
- Soft drinks
- Fruit juice
- Pickles
- Barbeque sauces
- Cosmetics such as medicated face washes and creams
- Sunscreen
- Aftershave
- Toothpaste

- Mouthwash
- Deodorant
- Cranberries, prunes, plums, cloudberries, and cinnamon

Bone broth can have collagen and glycine, but this depends on how it's made. However, it's quite difficult to get the necessary amount of either collagen or glycine from solely drinking bone broth. You would need to be eating more tendon meats, ligaments, and joint tissue with the skins instead of just methionine-rich muscle meat. Not only would that reduce food waste, but it also helps to balance your daily glycine-methionine ratio. Supplemental glycine is also a

good option because it's easy to consume.

Elastin is another collagenous protein found in connective tissues and about 33% of it is made of glycine. In adults, elastin turnover is quite low, but its demand significantly increases during pregnancy, which is why pregnant women need more glycine[370]. Periods of growth such as puberty and infancy also raise glycine demand. Patients with muscular dystrophy may greatly benefit from supplemental glycine and creatine[371],[372].

Here are the conditions that increase your glycine demand[373],[374],[375],[376],

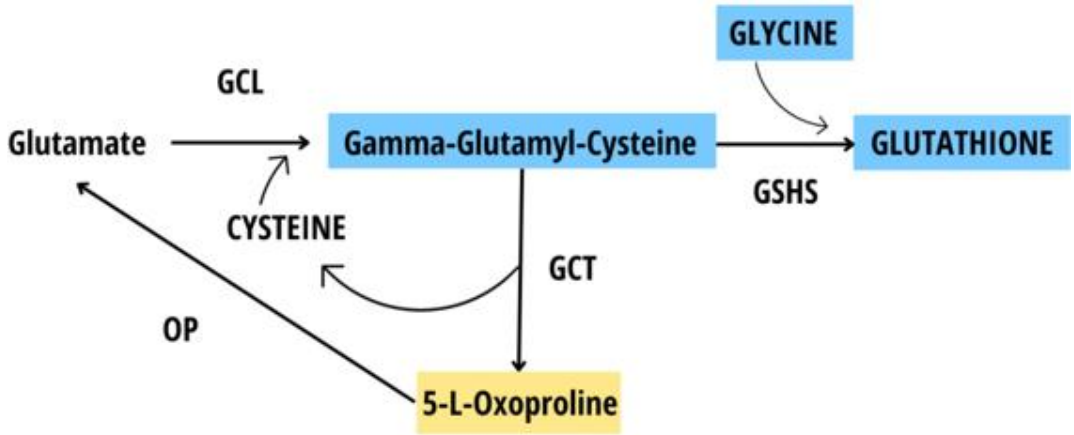
[377],[378],[379],[380],[381]:

- High physical activity and exercise
- Growth periods in children
- High levels of cortisol and inflammation
- Use of corticosteroids
- Malabsorption diseases (Celiac disease, Crohn's disease and ulcerative colitis)
- Myasthenia gravis (reduced ability to digest collagen/gelatin)
- Pregnancy
- Sickle cell disease
- Burns and wounds
- Medications (conjugation of drugs/xenobiotics for elimination)

- Muscular dystrophy and sarcopenia
- Being in an older age group
- Asthma
- Diabetes
- Hypertension

When glycine levels are inadequate, there is a higher excretion of 5-L-oxoproline in the urine. This can be an indirect indicator of glycine deficiency, although it's not 100% accurate[382]. When looking at 5-L-oxoproline levels as a marker of glycine deficiency, there needs to be enough cysteine, as there needs to be an overproduction of gamma-glutamyl-cysteine for 5-L-

oxoproline to form. Thus, the absence of 5-L-oxoprolinuria doesn't necessarily mean no glycine deficiency but it may if cysteine levels in the body are adequate. In normal adults on a mixed diet, the average excretion rate of 5-L-oxoproline is 27 umol/mmol creatine[383]. Higher levels than this may reflect glycine deficiency.[384]



Adapted From: Mélendez-Hevia et al (2009)

In conclusion, the modern world imposes an ever-greater demand for glycine. The limited amount our body can synthesize naturally is not enough for optimal collagen turnover and hence supplementing with 5-10 grams of glycine per day would greatly improve many aspects of health and longevity.

Chapter 4: Collagen for Joints, Tendons, Osteoarthritis & Osteoporosis

By now you should be familiar with collagen's importance for your body's structural integrity. Collagen scaffoldings are even used in tissue regeneration as well as supporting cells that build bones and connective tissues[385],[386],[387],[388],[389]. The triple helix structure of collagen also makes it perfect for building bones and tendons. In this chapter, we're going to look at all the conditions related to joints, tendinopathy, injuries, osteoarthritis, and osteoporosis.

The Epidemic of Tendinopathy and Tendon Ruptures: Could It Be Caused by a Lack of Collagen?

Tendinopathy is defined as a syndrome of tendon pain, tenderness and swelling that affects functioning[390]. It can even lead to tendon ruptures. Achilles tendon injuries occur most frequently in those playing soccer, tennis (or other racket games) and basketball[391]. So, if you play any of the above-mentioned sports you need to support the health of your Achilles tendons. **Achilles tendinopathy is a debilitating injury that affects 50%**

of distance runners in their lifetime[392]. Nearly half of endurance runners without Achilles tendon pain have pathological changes on imaging of the Achilles[393]. Thus, up to 1 out of 2 endurance runners may be at risk of an Achilles tendon rupture. In one study, 16% of young, healthy, active people had abnormal Achilles tendons and at least 1 abnormality on ultrasonography[394]. A substantial portion of athletes believe their performance is decreased because of tendon pain[395]. Additionally, around 4% of people with Achilles tendinopathy sustain an Achilles tendon rupture[396]. **It is thought that chronic degeneration**

of collagen in tendons leads to tendon rupture[397]. This is because multiple studies show degenerative changes in people with tendon ruptures with some studies showing a 100% prevalence[398].

Another contributing factor to tendinopathy is a lack of blood flow to tendons. Tendons and ligaments already lack proper blood flow. Thus, maintaining good arterial/capillary health and blood flow and focusing on tendon healing after repetitive microtrauma may help to prevent ruptures. Tendonitis and tendinopathy cause significant morbidity and cost to the healthcare system[399]. If you have any of the below symptoms it

could be an issue with your collagen health.

Symptoms of tendinopathy include[400]:

- Adductor related tendinopathy – **groin pain of the adductor tendons**
- Greater trochanteric pain syndrome – **lateral sided hip pain**
- Jumper's knee – patellar tendonitis – **inflammation of the patellar tendon**
- Achilles tendinopathy – **inflamed Achilles tendon**
- Plantar fasciopathy – **inflammation or**

thickening/degeneration of a band of tissue that connects the heel bone to the toes

Certainly, overuse increases the prevalence of tendinopathies[401]. However, **31% of patients with Achilles tendinopathy do not participate in vigorous physical activity**[402]. In other words, overactivity may only explain about 2 out of 3 Achilles tendinopathies, suggesting some other underlying factor such as metabolic and/or vascular issues. Regardless of the cause, **supplementing with collagen may be one of the best ways to prevent tendinopathies and tendon ruptures**

as collagen is what tendons are made of. Think of taking collagen like putting on body armor. For example, you could die from a gunshot or knife wound, but if you are wearing body armor you are protected. It doesn't matter if you're hit by a bullet or a knife-blade, the body armor is there to protect you regardless of the insult. So, while many factors contribute to collagen damage, the data shows that supplementing with collagen can help increase collagen health. Furthermore, **supplementing with collagen in clinical studies improves skin, nail and bone health, tendinopathy, osteoarthritis, osteoporosis, and pressure ulcers**[403],

[404],[405],[406],[407],[408],[409],[410],[411].

Supplementing with **collagen has even been shown to improve arterial stiffness, blood pressure and nitric oxide in those with elevated blood pressure**[412] and can increase muscle mass, muscle strength and fat loss in elderly sarcopenic men[413].

You already read about Dr. DiNicolantonio's injury to his pectoralis tendon when he was 26 years old, but what makes his case so interesting is that pectoralis tendon ruptures used to be rare. However, times are changing, and not for the better. **Of all the pectoralis injuries reported in the**

medical literature over the past 200 years, 75% have occurred in the last 30 years with about half being reported from the year 2000 or later[414]. Did humans spontaneously decide to lift heavier weights starting in the year 2000? Or is something else going on to increase these injuries? It's certainly possible that doctors are reporting more cases in the medical literature, but the increase in other tendon injuries suggests that something else is at play. For example, the incidence of Achilles tendon ruptures has dramatically increased[415],[416]. **In Finland**, over a 33-year period (1979 to

2011) **there has been a 10-fold increase in Achilles tendon ruptures** (2.1 to 21.5 per 100,000)[417]. In Denmark, the annual incidence of Achilles tendon ruptures has more than doubled (18.2 to 37.3 cases) from 1984 to 1996[418]. Thus, while many factors could be at play, we believe this is largely driven by a degeneration in collagen health. Essentially, **a population-wide collagen deficiency may be the cause of the increased incidence of tendon injuries.**

Indeed, **histological studies of Achilles tendinopathies show disorganized collagen structure, suggesting that**

tendinopathies and tendon ruptures are primarily a degenerative, non-inflammatory condition[419]. Biopsies of patients with Achilles tendinopathies also shows an increased number of matrix metalloproteinases (MMPs), which are enzymes that break down collagen and cause increased collagen turnover. The studies also reveal **smaller and thinner collagen fibrils** and an increased number of cells in the injured areas, again with no inflammation detected. The authors of the study concluded *"[…] the present data supports the notion that tendinopathy is an ongoing degenerative process."*[420] Although the authors did

admit that inflammation may be an initiating factor in tendinopathies, later it appears to be primarily a degenerative condition. Thus, to fix the degenerating collagen, we need to regenerate it and the best ways to do that is by:

(1) preventing further damage

(2) increasing collagen synthesis and strength and

(3) supplementing with glycine[421]

How to do this will be discussed in Chapters 2 and 3.

Osteoarthritis: Is it Due to Poor Collagen Health?

Osteoarthritis (OA) is the most common form of arthritis, affecting 237 million people, or 3.3% of the global population[422],[423]. It affects 1 out of 7 adults in the U.S. and is the 4th leading cause of disability globally[424],[425]. OA occurs when the protective cartilage that helps cushion your bones wears down, causing damage to the joints and inflammation[426],[427]. Osteoarthritis can affect any joint, but it is most common in the hands, knees, hips and spine[428]. Knee osteoarthritis occurs in an

estimated 37.4% of adults in the United States with around 1 out of 3 suffering from pain and functional limitations[429].

You may be asking yourself, *"How does collagen affect osteoarthritis?"* **It just so happens that cartilage is made of Type II collagen and damage to type II collagen is commonly found in osteoarthritis**[430]. A 2018 meta-analysis showed that **collagen supplementation is effective in improving osteoarthritis symptoms**[431].

Thus, **a possible fix for osteoarthritis** becomes a simple one:

(1) prevent further damage to your cartilage and

(2) repair/regrow new cartilage.

Below are some strategies that can help you do just that.

Most people use non-steroidal anti-inflammatory medications such as ibuprofen (Advil) or naproxen (Aleve) to manage their osteoarthritis pain but that is only a band-aid and doesn't treat the underlying cause of the cartilage loss/damage[432]. Moreover, most NSAIDs are associated with an increased risk of gastrointestinal bleeding, heart attack and stroke[433], [434],[435],[436],[437]. So, what can help patients with osteoarthritis that doesn’t

have severe side effects and helps the underlying issue?

There are several supplements that have good evidence for helping reduce pain and/or improve physical function in patients with osteoarthritis:

- Pycnogenol[438],[439]
- Turmeric or turmeric root extract[440],[441]
- Boswellia or boswellia serrata extract[442]
- Glucosamine[443],[444],[445],[446]
- Chondroitin[447],[448] or any combination thereof

- Methylsulfonylmethane[449],[450] (commonly abbreviated as MSM)
- BiovaFlex®, which is a water-soluble chicken eggshell membrane hydrosylate[451]
- Polycan™, a beta-glucan produced from black yeast[452]
- Q-Actin™ (an aqueous extract of cucumber)[453]
- Instaflex™ Joint Support [a joint pain supplement containing glucosamine sulfate, methylsufonylmethane (MSM)][454]
- White willow bark extract[455],[456]
- Ginger root concentrate[457]

- Cayenne or capsaicin[458]
- Hyaluronic acid[459]
- Hydrolyzed collagen peptides (type I and type II)[460],[461]
- Undenatured type 2 collagen (which is from cartilage)[462],[463].
    - Undenatured type 2 collagen may even help those with rheumatoid arthritis.[464]
- Hydrolyzed eggshell membrane[465],[466],[467],[468],[469].

Let's now take a closer look at all of them.

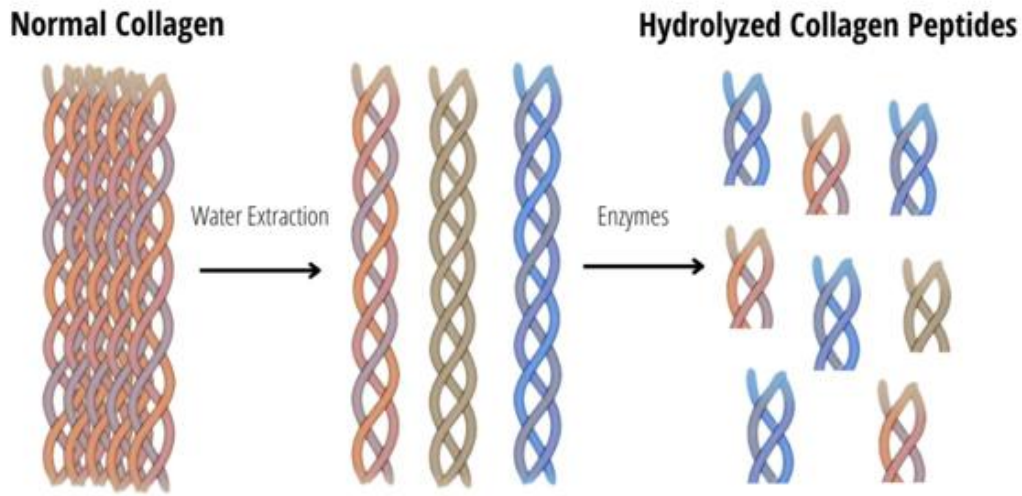
Hydrolyzed Collagen Peptides

There are 3 main types of hydrolyzed collagen on the market (type I, II and III). Bovine hydrolyzed collagen contains Type I and III, marine hydrolyzed collagen contains type I and chicken sternal hydrolyzed collagen is type II (important for cartilage and joint health).

The one issue with getting collagen from the diet alone is that it is not already broken down into smaller peptides, making it harder to absorb. **Hydrolyzed collagen or collagen peptides get absorbed better as small peptides**[470], [471]. Taking hydrolyzed collagen improves collagen health and synthesis in numerous bodily tissues including that

of cartilage[472],[473]. Some clinical studies have found that taking hydrolyzed collagen decreases joint pain, especially in those with the most severe symptoms[474],[475],[476],[477]. This is because **taking collagen leads to an accumulation of collagen in cartilage and at the same time stimulates the synthesis of type 2 collagen and proteoglycans**[478],[479]. These negatively charged proteoglycans, thanks to sulfate, hold onto water and help cushion our joints. In vitro and mouse studies have shown that hydrolyzed collagen peptides influence the growth of fibroblasts, which are a

type of cell that synthesize collagen and the extracellular matrix[480],[481]. Collagen peptides (5 grams a day) combined with resistance training leads to greater hypertrophy in tendinous and muscular structures of the Achilles tendon than resistance training alone in young physically active men[482].



Undenatured Type 2 Collagen (UC-II)

Taking low doses of undenatured type 2 collagen derived from cartilage appears to have a different mechanism of action compared to taking higher dose of collagen peptides (which are normally composed of type I bovine collagen). Taking the low doses of undenatured type 2 collagen (UC-II) facilitates oral tolerance to the antigen and reduces immune cell attack on joint cartilage[483]. The type 2 collagen must be undenatured, which provides active epitopes with the correct three-

dimensional structures to Peyer's patches, which influences the signaling required for the development of immune tolerance. **Basically, what you are doing is presenting low doses of undenatured type 2 collagen to the immune system, so it becomes tolerant to it and stops breaking down your type 2 collagen in cartilage between your joints.** It's a marvelous way to trick the immune system and start healing your own cartilage. In rats, undenatured type 2 collagen reduces inflammation and articular cartilage damage[484]. Human clinical studies have also shown UC-II to be effective in

rheumatoid arthritis and osteoarthritis[485],[486],[487],[488].

Glucosamine

Glucosamine is required for the synthesis of cartilage glycosaminoglycans (GAGs)[489], which act as lubricants or shock absorbers[490], [491]. Osteoarthritic cartilage GAGs appear to have decreased sulfate content[492]. Thus, glucosamine sulfate specifically is the best form of glucosamine to take. **Glucosamine has many trials showing efficacy for osteoarthritis**[493]. Exercise also

improves cartilage GAG content, improving joint function[494].

Glucosamine enters the cells via glucose transporters and is rapidly converted to UDP-N-acetylglucosamine, which serves as a substrate in the synthesis of hyaluronic acid and mucopolysaccharides and helps with the glycosylation of proteins[495]. An increase in these substances is why glucosamine is thought to benefit patients with osteoarthritis as it increases the cushioning factors between the joints. This is also perhaps why it takes several weeks to begin to feel the benefits of glucosamine. **The daily dose of**

glucosamine that provides the most benefit is likely above 1,500 mg, which seems to sit at the edge of demonstrable efficacy[496]. A more optimal therapeutic dose of glucosamine is likely around 1.5-3 grams twice daily[497]. However, most studies have under-dosed glucosamine, which is probably why the evidence is so controversial. Patients with elevated intraocular pressure or the elderly need to be careful with glucosamine as it may increase intraocular pressure[498]. However, other studies have not found an increase in intraocular pressure after

6 months of glucosamine sulfate taken at 1,500 mg per day[499].

Besides osteoarthritis, glucosamine supplementation has other benefits for overall longevity. It's been discovered that supplementing glucosamine is associated with a 39% decrease in total mortality among 16,686 U.S. subjects[500]. In the UK, among 466,039 subjects without cardiovascular disease, habitual use of glucosamine has been linked to a lower risk of cardiovascular disease events[501]. The reason for that is glucosamine's anti-inflammatory effects. Glucosamine sulfate contains sulfur, which is a component of

chondroitin in bones and cartilage[502]. Sulfur is also required for glutathione production[503],[504],[505], which is the master antioxidant of the human body[506]. Glutathione helps to lower inflammation and oxidative stress, improving symptoms of osteoarthritis as well[507],[508].

Instaflex™ Joint Support

Instaflex™ Joint Support is a joint pain supplement containing glucosamine sulfate, methylsufonylmethane (MSM), white willow bark extract, ginger root concentrate, boswellia serrata extract, turmeric root extract, cayenne, and

hyaluronic acid. In a double-blind placebo-controlled trial in 100 men and women (ages 50-75) having a history of joint pain, Instaflex™ significantly improved joint pain severity and improved the ability to perform daily activities and stiffness scores[509].

Pycnogenol

Pycnogenol is an extract from the bark of the French maritime pine, rich in polyphenols. It is primarily composed of procyanidins and phenolic acids. Pycnogenol contains 65-75% procyanidins[510]. Its procyanidins are biopolymers of catechin and epicatechin,

such as monomeric catechin, taxifolin and oligomers, consisting of catechin and epicatechin units with 7 or more flavonoid subunits[511]. Pycnogenol's phenolic acids are derivatives of benzoic and cinnamic acids and include caffeic and ferulic acid. The ferulic and caffeic acid and taxifolin are rapidly absorbed after 30 minutes, whereas the procyanidins are absorbed slowly, making pycnogenol both a short and long-acting anti-inflammatory/analgesic substance. Pycnogenol also has antioxidant, anti-platelet, and anti-thrombotic properties[512],[513], which makes it a very promising supplement for

those with cardiovascular disease, coronary artery disease or type 2 diabetes[514],[515],[516],[517].

Pycnogenol acts as both an antioxidant booster, doubling the synthesis of endogenous antioxidant enzymes in several cell systems, and a potent free radical scavenger[518]. It also protects against ultraviolet (UV) radiation-induced erythema (or redness) [519],[520]. Pycnogenol increases the activity of endothelial nitric oxide synthase, the main enzyme in your endothelial cells that produces the vasodilating gas nitric oxide[521]. This gives pycnogenol the ability to dilate

small blood vessels helping to improve microcirculation in diabetics and patients with cardiovascular disease. It also has mild antihypertensive effect. Pycnogenol can even help with premenstrual symptoms due to the spasmolytic action of some of its phenolic acids[522].

In patients with metabolic syndrome, pycnogenol has been shown to decrease waist circumference, triglycerides, blood pressure, fasting glucose and increase HDL[523]. Other benefits of pycnogenol include improving leg edema in patients with chronic venous insufficiency, reducing the incidence of deep vein thrombosis during long flights and

enhancing the healing of venous ulcers and hemorrhoidal episodes[524]. Pycnogenol has even been shown to improve varicose veins[525], benign prostatic hypertrophy[526], cognition, attention, and mental performance[527], [528],[529],[530],[531], allergies[532], and allergic asthma[533].

Regarding osteoarthritis, pycnogenol reduces pain, stiffness and improves mobility and at the same time reduces the use of NSAIDs[534],[535]. These benefits may be due to the anti-inflammatory actions of pycnogenol. Its constituents and metabolites such as

ferulic acid, caffeic acid and its active M1 metabolite get into the synovial fluid providing a direct anti-inflammatory effect[536]. Indeed, pycnogenol has been found to lower plasma free radicals and C-reactive protein in patients with osteoarthritis[537]. Pycnogenol also inhibits the release of the master switch of inflammation, known as nuclear factor-kappa beta (NF-KB), and MMP-9, a cartilage degrading proteolytic enzyme from activated monocytes[538]. This helps to reduce the overall inflammatory and degenerative process in osteoarthritis. A randomized trial in humans confirmed that **pycnogenol decreases the gene**

expression of various cartilage degrading substances in cartilage cells, including MMP3, MMP13 and IL-1B[539]. In serum, the levels of aggrecanases, which destroy the cartilage building block aggrecan, were also reduced. Thus, pycnogenol has both systemic anti-inflammatory effects and direct local effects for protecting cartilage breakdown.

Three clinical trials in humans have found significant benefit with the use of pycnogenol in patients with osteoarthritis. In these studies, pycnogenol was able to reduce pain (-40 to -45%), stiffness (-35 to -53%) and

improve physical performance (+22 to +56%). In two of the three studies the overall global score was recorded and improved by 49 to 50%[540],[541],[542]. Use of NSAIDs was significantly reduced in all three studies in the pycnogenol group, whereas there was a slight increase in the intake of NSAIDs in the placebo group. Despite a reduced intake of NSAIDs with pycnogenol, there was significant improvements in symptoms of mild osteoarthritis. Moreover, gastrointestinal complications and days spent in the hospital were reduced by approximately 60% in the pycnogenol group due to a reduction in the intake of NSAID use. **An effective daily dose of**

pycnogenol for improving osteoarthritis symptoms ranges from 100-200 mg per day, which is generally split into two or three doses and taken with meals.

Turmeric

Turmeric is a flowering plant of the ginger family. It is a common spice and the main ingredient in curry. Turmeric has been used for centuries in India and China as a treatment for skin diseases, infections, stress, and depression. Its primary active ingredient is curcumin, which gives turmeric its yellow color. Curcumin has anti-inflammatory, antioxidant, antimicrobial, antiseptic, antimutagenic,

hepatoprotective, and immunostimulating properties[543].

The curcuminoids in turmeric reduce inflammation such as interleukin-6 (IL-6) [544], tumor necrosis factor-alpha (TNF-alpha)[545] and c-reactive protein (CRP) [546]. This is likely why **turmeric has been found to reduce pain and oxidative stress in at least three randomized placebo-controlled trials in patients with osteoarthritis of the knee**[547],[548],[549]. Taking 2 grams of turmeric per day has also been found to be as effective as ibuprofen in knee osteoarthritis[550]. Taking 1.5 grams of

turmeric extract per day was also found to be as effective as ibuprofen with the added benefit of fewer gastrointestinal adverse events[551]. Thus, the overall evidence suggests that turmeric can be an effective alternative to NSAIDs with potentially fewer side effects. Additionally, if boswellia is added to turmeric (a combination of turmeric and boswellia at 500 mg twice daily) it can be more effective compared to a leading NSAID (celecoxib, brand name Celebrex) for the treatment of knee osteoarthritis[552]. Taking NSAIDs increases the risk for gastrointestinal bleeding and potentially increases the

risk of a heart attack and stroke. Thus, turmeric may be a safer alternative in those suffering with osteoarthritis and adding boswellia could make it more effective than NSAIDs.

The amount of curcumin in turmeric powder isn't that high – only about 3.14% by weight[553]. Thus, one teaspoon of turmeric powder can give you roughly 0.15 grams of curcumin, which is what people in India are estimated to consume per day[554]. However, curcumin in turmeric has poor absorption. Thus, many people combine it with black pepper or take a turmeric supplement with added piperine (the active ingredient

in black pepper) which increases curcumin's absorption by 2000%[555]. In general, around 1/4th of a teaspoonful of black pepper is used per teaspoon of turmeric. However, black pepper may increase the risk of intestinal damage and bleeds and should be used with caution[556]. Important to note is that piperine and turmeric can have medication interactions. Thus, you should always talk to your doctor prior to taking. However, if you are not taking medications, there seems to be little risk with this natural substance. Curcumin is also fat-soluble, which is why you should consume it with some fat.

It’s important to recognize that other components of turmeric, besides curcumin, provide benefits. In fact, curcumin-free turmeric exhibits anti-inflammatory, antidiabetic, and anticancer activities[557]. Elemene, which is derived from turmeric, is approved in China for the treatment of cancer. Other components of turmeric that may provide benefit include turmerin, turmerone, elemene, furanodiene, curdione, bisacurone, cyclocurcumin, calebin A, and germacrone[558]. Turmacin® is the water-soluble polysaccharides (called turmerosaccharides) from turmeric. It is complimentary to the fat-soluble

curcuminoids from turmeric and works synergistically against inflammation. There are several studies showing that Turmacin® helps with knee joint pain and knee osteoarthritis[559],[560],[561] and reduces pain and inflammation during exercise, which may increase exercise duration and help to preserve muscle function[562].

Methylsulfonylmethane (MSM)

Methylsulfonylmethane, or MSM, is an organosulfur molecule that is formed from dimethylsulfoxide (DMSO) and naturally present in the human body. MSM has anti-inflammatory properties

that are thought to help with osteoarthritis[563],[564]. However, it may also have anti-cancer, anti-atherosclerotic and free radical scavenging capabilities[565]. **Two randomized controlled trials in humans have found that MSM provides relief in osteoarthritis knee pain**[566],[567],[568]. The optimal therapeutic dose of MSM, with the least amount of side effects, appears to be around **1.7 grams twice daily**[569]. More studies are needed to better understand the efficacy and safety of MSM, however some patients may find some benefit from taking it. The FDA has declared

MSM as generally recognized as safe (GRAS).

Glycine

As we've already shown, there's a decline in collagen synthesis in osteoarthritis[570],[571]. High glycine concentrations stimulate collagen synthesis in cartilage cells, making glycine deficiency a potential driver of osteoarthritis[572]. Glycine has osteoprotective effects[573], improving the remodeling process of tendon cells[574] and helping in the recovery of tendinitis[575].

Eggshell Membrane

Eggs are highly nutritious foods, but they don't have a lot of collagen or glycine. However, eggshells themselves are quite rich in collagen. Eggshell membrane (ESM), specifically, has similar anti-osteoarthritic effects as collagen peptides. **Supplementing with ESM, 500 mg once a day, can significantly reduce joint pain and stiffness associated with osteoarthritis**[576],[577],[578],[579],[580]. Those effects kick in within 7-30 days and last at least 90 days[581]. Even dogs with suboptimal joint function benefit from ESM[582]. The benefits

appear to be dose-dependent with a 500 mg dose reducing perception of pain by 1.1 points more than a 300 mg dose[583]. Natural eggshell membrane suppresses tumor necrosis factor-alpha (TNF-alpha) and other inflammatory markers like NF-kB[584],[585]. In the gut, eggshell membrane powder can reduce inflammation by repairing the epithelium and decreasing microbial dysbiosis[586]. Eggshells themselves have antimicrobial proteins and peptides[587].

Besides joint pain and arthritis, ESM can also improve skin health and wrinkles[588]. Supplementing 450 mg/d of hydrolyzed eggshell membrane for 12

weeks improves facial skin and hair appearance[589]. Hydrolyzed eggshell membrane supports skin fibroblasts[590] and regulates cellular functions involved with wound healing[591].

Hyaluronic Acid

Hyaluronic acid (HA) is a compound that helps to lubricate the joints and fascia by making them hold onto more water[592],[593],[594],[595]. The FDA has approved the treatment of knee osteoarthritis with intra-articular injections of hyaluronic acid[596],[597]. A 2020 meta-analysis concluded that intra-articular injections of high molecular

weight HA improve pain and function in patients with knee osteoarthritis[598]. **Taking 200 mg of HA once a day for 12 months alleviates symptoms of knee osteoarthritis**[599].

Hyaluronic acid has a role in tissue regeneration, wound healing, inflammation, and angiogenesis (growth of new blood vessels)[600]. However, evidence of its effects is still limited. HA can also moisturize the skin[601], making it interesting for its cosmetic effects. The epidermis' basal layer contains relatively large amounts of hyaluronic acid[602]. UV

radiation from the sun degrades hyaluronic acid[603].

The average person weighing around 150 lbs. (70 kg) has 15 grams of hyaluronic acid in the body, of which 1/3rd is degraded and synthesized daily[604]. With age, the chain size of HA in cartilage decreases, but its amount increases, suggesting a decrease in structure/quality of HA with age.[605]

Chapter 5: Cardiovascular Disease: The Vitamin C-Collagen Connection

Cardiovascular disease (CVD) is the leading cause of death worldwide[606]. In 2015, CVD contributed to 32.1% of all deaths – a continuous rise from the 25.8% in 1990[607],[608]. That means **around 1 out of 3 people died from cardiovascular disease**. In men, coronary artery disease (CAD) and strokes account for 80% of CVD deaths and in women 75%[609]. What's even more profound, is that **up to 90% of**

heart disease is preventable[610],[611]. **Dietary factors are thought to contribute to 53% of all CVD deaths**[612]. Essentially, excess calorie consumption, trans fats, refined carbs/sugars, omega-6 seed oils and alcohol may cause one out of every two CVD deaths[613],[614],[615],[616],[617],[618],[619],[620],[621],[622],[623],[624],[625],[626],[627],[628],[629]. Metabolic syndrome, obesity, hypertension, diabetes and poor sleep also promote heart disease[630],[631],[632],[633]. In the scope of this chapter, we will focus on the connection of collagen and vitamin C with cardiovascular diseases.

The Role of Collagen and Vitamin C in Cardiovascular Disease

The primary driver of heart disease is atherosclerosis, which is plaque that builds up in the artery wall[634]. These plaques are made of fat, cholesterol, calcium, and other substances. Some of these plaques can become so large that they limit blood flow and oxygenation to different parts of the body, which can even lead to a heart attack or stroke. However, most of the time, heart attacks and ischemic strokes are due to the rupturing of smaller unstable plaques, causing blood clots. By the age of 65,

almost everyone is affected with atherosclerosis to a certain degree[635]. Although atherosclerosis was first described in 1575, it's been found to have occurred in humans as far back as 5,000 years ago[636]. Risk factors for atherosclerosis are high blood pressure, inflammation, diabetes, smoking, obesity, and oxidation of low-density lipoprotein cholesterol (LDL-C)[637],[638],[639].

Back when the study of atherosclerosis was primarily dependent on autopsy, a Canadian pathologist named **J.C. Paterson suggested that strokes and heart attacks were caused by increased capillary fragility and**

rupture of capillaries in the artery[640]. He believed a combination of degeneration of the capillary tissue and hypertension were the main culprits of cardiovascular disease as they would cause increased intra-capillary pressure, capillary bleeding and atherosclerotic plaque formation and rupture. Paterson believed that calcification of atherosclerotic plaque was a protection against the capillary bleeding and that it was the latter that lead to heart attacks and ischemic strokes - and he seems to be correct.

Essentially, **Paterson believed that strokes and heart attacks were due to**

two primary factors: (1) high blood pressure (either transient or persistent) and (2) capillary fragility. Both of those combined would lead to capillary rupture, bleeds, and subsequent clots or occlusions causing heart attacks or ischemic strokes. However, the most important point was that **he believed that capillary fragility was due to vitamin C deficiency[641].** Vitamin C not only helps the body make collagen, but it strengthens collagen. In other words, vitamin C and collagen health determines the health of our capillaries, and if these capillaries are fragile, they can rupture, which can lead to heart attacks and strokes.

Take home message?

A deficiency in vitamin C and/or collagen may be a leading cause of strokes and heart attacks causing millions of deaths every year.

In his 1941 publication entitled *"Some factors in the causation of intimal haemorrhages and in the precipitation of coronary thrombi"* J.C. Paterson wrote (slightly paraphrased),

> *"…increased viscosity and coagulability of the blood, without the primary injury to the arterial wall is doubtful to cause thrombus formation…**intimal hemorrhage (bleed, our insertion) is admitted***

now to be the common precipitating cause of coronary thrombosis"[642]

He went on to write:

"In a report in 1936 and in subsequent reports, I showed by serial sections that intimal haemorrhages (bleeds, our insertion) in coronary arteries are intrinsic lesions. […] The haemorrhages were found to be due to the ***rupture of capillaries*** *which are derived from the coronary lumen. This finding was confirmed and elaborated upon by Wartman, Winternitz and his co-workers, and Horn and Finkelstein.*

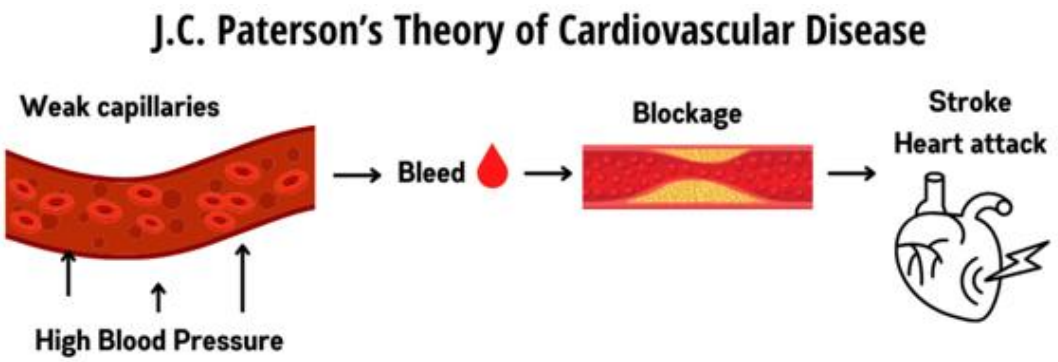
Intimal capillaries are not normal structures; they are found only in sclerotic arteries, and they develop, apparently, in response to the demand for nutrition by the plaques of atherosclerosis in which they ramify. *They are not related to the usual vasa vasorum although they do anastomose with these structures in some cases."* [643]

*"**The rupture of intimal capillaries and the subsequent formation of intimal haemorrhages is a fairly common finding in sclerotic coronary arteries**; and it may lead to a variety of sequelae as follows (1)*

Occasionally a small ***intimal haemorrhage*** *which is otherwise innocuous may irritate the medial coat and* ***result in spasm and acute coronary insufficiency****. (2) In a few cases (13 percent in my series)* ***the haemorrhage attains such a size that the coronary lumen is obstructed by pressure, and sudden death from coronary insufficiency results****. (3) In approximately one-third of the cases the only results is a slight increase in the size of the atherosclerotic plaque, first from the addition of blood to its bulk, and later from the presence of products of repair. (4) Finally,* ***in***

about half the cases secondary thrombosis occurs in the coronary lumen." [644]

Essentially, Paterson was saying that **weak capillaries would rupture causing a bleed, which would then induce clots causing strokes/heart attacks**. Thus, it is a bleed that causes occlusion (blockage) in the arteries feeding the heart and brain. So, what causes weak capillaries? You guessed it, **vitamin C + collagen deficiency**. Additionally, **a deficiency in copper and vitamin A** would also contribute to weak capillaries (as both are important for collagen health).



One of the most compelling writings of Paterson in his 1941 paper was the following:

> ***"Since 1935 fifty-eight fatal cases of coronary thrombosis have been studied*** *by fairly exhaustive methods, including serial sections in most instances, and* ***in 52 cases, or 89 percent, an intimal haemorrhage has been found at the site of precipitation of the thrombus.*** *Recently Horn and Finkelstein have*

confirmed this finding in a larger series. ***It appears certain, therefore, that intimal haemorrhage (or other sequelae of capillary rupture) is the usual precipitating lesion in coronary thrombosis****.”* [645]

Again, it seems to be a hemorrhage (bleed) in the capillaries of atherosclerotic plaque that leads to clots in the arteries and subsequent heart attacks and strokes.

Paterson concluded with the following note:

“In the final analysis then, ***the factors responsible for the rupture of***

intimal capillaries are the immediate causes of precipitation of most coronary thrombi*. Three distinct sets of factors are involved in the process…The integrity of a capillary wall in any part of the body depends on (1) the pressure of blood within the lumen, (2) the strength and elasticity of the wall, and (3) the rigidity of the supporting tissue. I am presenting evidence here that suggests that hypertension (persistent or transient),* ***increased capillary fragility due to avitaminosis C*** *(lack of vitamin C, our insertion), and inadequate calcification of atheromatous foci are*

concerned in the formation of intimal hemorrhages." [646]

Shedding more light on vitamin C, Paterson wrote:

[…] ***a striking feature in the series was the low concentrations (of vitamin C,*** *our insertion)* ***noted in most of the patients with signs and symptoms of coronary occlusion,*** *81 percent of the cases, showing a concentration below 0.5 mg. percent. This* ***high incidence of vitamin C deficiency*** *was not reached by any other type of disease in the series. Even gastro-intestinal diseases, including peptic ulcer, showed a*

higher vitamin C level on the average than did coronary occlusion, and this is surprising when one considers the effect of gastro-intestinal dysfunction on diet."[647]

The vitamin C/collagen theory of heart disease makes complete sense. **Scurvy, or vitamin C deficiency, can even lead to symptoms of coronary thrombosis thought to be due to hemorrhage in the heart muscle**[648]**.** Vitamin C is also beneficial for lowering blood pressure and improving endothelial health[649], [650]. So, from the perspective of lowering blood pressure, improving artery health and strengthening capillaries, vitamin C

is extremely important for protecting against a heart attack or stroke. However, this only explains the rupture of the capillaries and the formation of the clot. This theory doesn't explain the cause of atherosclerotic plaques in the first place. It just so happens that some authors have noted that **atherosclerosis is a *"localized cellular ascorbate (vitamin C, our insertion) deficiency"***[651]. Vitamin C is important for recycling tetrahydrobiopterin, which is a necessary cofactor for endothelial nitric oxide synthase (the main enzyme that makes nitric oxide in our endothelial cells). In other words, **vitamin C helps keep nitric oxide levels elevated,**

which in turn helps reduce atherosclerotic plaque formation.

So, if vitamin C is important for preventing atherosclerosis, does giving vitamin C help patients who already have it? It turns out that it might.

In 1954, G.C. Willis performed arteriography on the femoral artery in 15 patients, 10 patients got vitamin C at a dose of 500 mg three times a day, the other 5 patients did not. **In the patients who got vitamin C, 6 out of 10 had smaller plaques after supplementation, whereas there was no regression of atherosclerotic plaques in the control patients.** Also,

actual symptoms of atherosclerosis such as angina, claudication and painful xanthomas were reduced in those given supplemental vitamin C.[652]

Regardless of the cause of the atherosclerotic plaque, if you can prevent the capillary bleeds, which is what Paterson believed was the cause of clots/vasospasms that can kill you, then it doesn't matter what caused the plaque in the first place - preventing or reversing atherosclerotic plaque simply becomes a bonus.

It's important to note that we believe that it is always best to get vitamin C from the diet, or as close to a dietary

source as possible. This is because vitamin C works in concert with other vitamins and minerals to strengthen collagen and reduce oxidative stress. In other words, vitamin C doesn't work very well if your vitamin E, selenium, copper, sodium, iron, or zinc status is suboptimal. Additionally, most studies that fail with supplemental vitamin C, only give it once per day and typically at doses lower than 500 mg/day, whereas studies tend to find positive results when vitamin C is dosed more frequently, especially when the total daily dose is 500 mg or higher[653], [654]. You wouldn't expect to breathe all your oxygen once per day, nor would you

be expected to drink all your water once per day. Thus, vitamin C should not be ingested just a single time per day, it should be ingested multiple times per day. This is how vitamin C would have been consuming during evolutionary times when we received it from both animal and plant sources. In fact, **the pharmacokinetics of vitamin C indicate that it should be dosed every 2-3 hours to maintain elevated blood concentrations**[655],[656].

Vitamin C is an essential vitamin with an RDA of 90 mg/d for adult males and 75 mg for adult females[657]. To prevent scurvy, you only need about 7-10 mg per

day. However, to fully saturate the entire body for *optimal* antioxidant status, you'd need up to 1,000 mg of vitamin C per day (preferably 500 mg in 2 doses) or more[658]. In other words, there can be up to a 100-fold difference in a vitamin C intake that would prevent deficiency (10 mg/day) and an optimal intake (1,000 mg/day). Daily optimal intake of vitamin C has been suggested to be 120-200 mg[659],[660]. Vitamin C given twice a day at 500 mg is likely needed to fully saturate tissues, especially in the elderly or people under a lot of stress[661]. You don't have to supplement vitamin C daily, but you should be consuming foods that

contain vitamin C every day. A high intake of fruits and vegetables is associated with reduced cardiovascular disease[662],[663]. Eating at least 5 servings of different fruits and vegetables can provide you with around 200 mg of vitamin C.

Here are the highest sources of vitamin C from whole foods:[664]

Food	**Mg per serving**
Red pepper, ½ cup	95
Orange juice, ¾ cup	93
Orange, 1	70

medium	
Grapefruit juice, ¾ cup	70
Kiwifruit, 1 medium	64
Green pepper, ½ cup	60
Broccoli, ½ cup	51
Strawberries, ½ cup	49
Brussels sprout	48
Tomato juice, ¾ cup	33

Cantaloupe, ½ cup	29
Cabbage, ½ cup	28
Potato, 1 medium	17
Tomato, 1 medium	17
Spinach, ½ cup	9
Green peas, ½ cup	8

Vitamin C can inhibit or enhance copper absorption, depending on when you consume it. If you take vitamin C prior to (about 75 minutes beforehand) or

together with copper, it decreases copper absorption by blocking copper's binding to metallothionein. However, if you take vitamin C after ingesting copper (75 minutes afterward), it promotes ceruloplasmin and lysyl oxidase activity. Vitamin C also helps to initiate the transport of copper ions into cells[665]. Taking large doses of vitamin C may increase the need for copper[666]. Thus, copper intake should be optimized on a high vitamin C intake. Fortunately, whole food plant foods generally contain some copper and vitamin C to help with collagen synthesis[667]. When you think about collagen health you should always

think about vitamin C, copper, vitamin A and sodium. This is because sodium helps with vitamin C absorption in the gastrointestinal tract. Sodium is also needed to drive active vitamin C into our tissues. **Having low sodium levels in the blood can reduce vitamin C that is driven into tissues, which has been shown to lead to decreased collagen health and bone disease[668].** This is because two sodium ions are required to bring one ascorbic acid (vitamin C) molecule into the cell. Lastly, copper is needed for the lysyl oxidase enzyme, which cross-links collagen and makes it strong, and vitamin A is needed to move copper around the body. So, whenever

we are talking about collagen health, always think of these four nutrients, 1.) **vitamin C**, 2.) **copper**, 3.) **vitamin A** and 4.) **sodium** in addition to obtaining collagen from the diet.

Glycine in Heart Disease and Ischemia Reperfusion Injury

Glycine has many beneficial effects around heart disease, stroke, and atherosclerosis, primarily through reducing inflammation and increasing glutathione[669],[670],[671],[672].

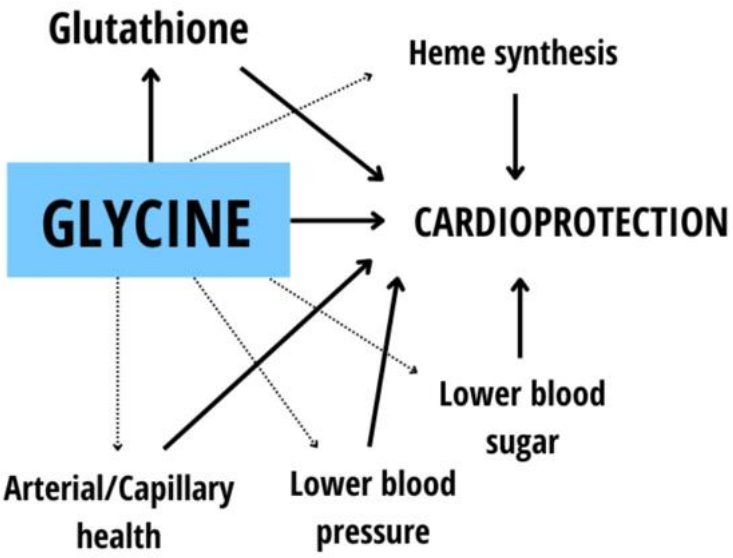
Supplementing the diet with n-acetylcysteine (NAC) and glycine, both components of glutathione, in old mice improves diastolic function[673]. Patient who have suffered a heart attack have low plasma glycine levels[674].

In human coronary arterial endothelial cells, glycine, cysteine, and histidine

exhibit anti-inflammatory effects[675]. Vascular endothelial growth factor (VEGF) signaling requires glycine to promote the growth of new blood vessels or angiogenesis (important in the formation of collaterals to circumvent blood flow when there are blockages in the coronary arteries)[676]. Glycine also helps to balance methionine levels, which in excess can raise homocysteine and promote cardiovascular disease[677], [678]. Furthermore, glycine protects against the toxic effects of oxidized oils[679], which can also oxidize cholesterol and raise inflammation.

Glycine's role in heart disease[680],[681],[682],[683],[684]:

- Prevent tissue injury
- Promote antioxidant capacity
- Promote collagen synthesis and wound healing
- Improve immune function
- Help metabolic disorders such as diabetes, obesity, ischemia-reperfusion injury, and various inflammatory conditions
- Reduces platelet aggregation



The decrease in vascular function and blood flow seen in cardiovascular disease tends to promote ischemia and hypoxia (lack of blood flow and oxygenation in tissues, respectively)[685]. Ischemic heart disease is the top cause of death in Western countries[686]. An ischemic stroke is usually the result of a blood clot blocking blood flow in the brain[687]. Glycine is necessary for the

formation of heme and hemoglobin and thus oxygenation of cells[688]. It's been shown in both in vitro and in vivo ischemia models that having low glycine levels is harmful in post-ischemic injury, whereas high levels of glycine exert neuroprotective effects by activating glycine receptors[689]. Giving glycine prior to ischemia/reperfusion ameliorates mitochondrial dysfunction and provides mitochondrial protection in rats[690]. Glycine administration maintains mitochondrial activity and reduces ischemic-reperfusion injury[691]. Glycine protects heart muscle cells from high glucose and hypoxia induced injury by

improving mitochondrial function[692]. Glycine also protects the liver from ischemia reperfusion injury[693]. Both glycine and taurine protect against fatty liver by reducing oxidative stress from immune cells called Kupffer cells[694].

Patients with type 2 diabetes have glutathione deficiency[695]. Glutathione synthesis is decreased in diabetic patients, which can be restored with cysteine and glycine supplementation[696]. Plasma glycine levels are low in obese and/or diabetic patients, however, improving insulin resistance increases their plasma glycine

concentrations[697]. There's a lot of evidence suggesting **glycine improves insulin sensitivity and glucose homeostasis through enhancement of insulin secretion**[698],[699],[700],[701],[702]. Serum glycine levels are associated with body fat, abdominal obesity, and insulin resistance[703].

Metabolic syndrome is a pathological condition wherein ≥ 3 of the following is present: high blood pressure, central obesity, high fasting triglycerides, high fasting blood sugar and low HDL cholesterol[704]. Metabolic syndrome doubles the risk of cardiovascular disease and increases all-cause mortality

by 1.5-fold[705],[706]. Up to 34% of people in the U.S. have metabolic syndrome[707]. **In older adults, glycine levels are inversely associated with metabolic syndrome and cardiometabolic traits[708]. Supplementing with glycine improves metabolic syndrome, including diabetes, obesity, hyperlipidemia, and hypertension[709],[710],[711].** Glycine increases adiponectin and IL-10 expression in fat cells, which exerts anti-inflammatory and fat burning effects[712]. Adding 1% glycine to drinking water that contains 30% sucrose to rats with metabolic syndrome for 8 weeks reduces

blood pressure, triglycerides, insulin levels, HOMA-IR index, and inflammation[713]. Among a population of Mediterranean males, a high branched-chain amino acid (BCAA) pattern, including leucine, isoleucine, valine, appears to be positively associated with cardiometabolic risk factors and metabolic syndrome, whereas the glutamine/glycine/serine/asparagine pattern is inversely associated[714]. This may indicate that a higher intake of collagenous proteins (tendons, ligaments, skins, gelatin, glycine) favors lower cardiovascular risk.

Here are some guidelines for assessing metabolic syndrome:

- **Fasting Insulin**: Normal range: 3-8 uIU/mL (18–48 pmol/L); moderate insulin resistance: 8-12 uIU/mL (48-72 pmol/L); severe insulin resistance: > 12 uIU/mL.
- **Fasting Blood Sugar:** Normal ranges: < 100 mg/dl (5.3 mmol/L), prediabetes: 100-125 mg/dl (5.6-6.9 mmol/L), diabetes: > 126 mg/dl (7 mmol/L).
- **Blood pressure:** Normal blood pressure is < 120/80 mmHg. 130-139/80-89 mmHg is considered stage 1 hypertension. Stage 2 hypertension is ≥ 140/90 mmHg.
- **Triglycerides**: Normal range: < 150 mg/dl (1.7 mmol/L); borderline-high levels: 150-200 mg/dl (1.8 to

2.2 mmol/L); high levels: 200-500 mg/dl (2.3 to 5.6 mmol); very high levels: > 500 mg/dl (5.7 mmol/L or above).

- **HDL Cholesterol:** Normal fasting HDL is between 40-60 mg/dl. Optimally, it should be between 50-80 mg/dl. HDL < 40 mg/dl can be problematic and a sign of either dyslipidemia or metabolic syndrome.
- **Triglyceride to HDL Ratio**: Normal range: 1.0 +/- 0.5; moderate insulin resistance: 2-3; severe insulin resistance: > 4.
- **A1C (average 3 month blood sugar):** Normal range: ≤ 5.6% (≤ 38 mmol/mol); prediabetes: 5.7-6.4% (> 39-46 mmol/mol); diabetes: ≥ 6.5% (> 47 mmol/mol).

- **HOMA-IR (Homeostatic Model Assessment for Insulin Resistance)**: Normal range: (0.5-1.5); moderate insulin resistance: 1.5-2.5; severe insulin resistance: > 3.0
- **Body Fat Percentage**: Normal range: 5-20% for men and 10-25% women. Anything above 20-25% is an excess amount of fat for men and women, respectively.
- **Waist to Hip Ratio**: Optimal ratio for women is < 0.80 and for men < 0.95. Moderate risk for women is 0.81–0.85 and for men 0.96–1.0. High risk for women is > 0.86 and for men > 1.0. A waist circumference over 40 inches (men) or 35 inches (women) is problematic and increases risk of

heart disease, diabetes, and premature death[715].

Health risk with W/H ratio	Women	Men
Low	0.80 or lower	0.95 or lower
Moderate	0.81–0.85	0.96–1.0
High	0.86 or higher	1.0 or higher

Metabolic syndrome and diabetes may begin in the liver, with the accumulation of visceral fat in and around the organs[716],[717],[718]. Thus, keeping the liver healthy and lean is essential for

overall health. That means limiting alcohol, fructose, and refined sugar intake[719],[720],[721],[722]. Glycine has many beneficial properties surrounding the liver, primarily around protecting against oxidative damage and liver injury[723],[724],[725],[726],[727],[728]. In rats, glycine protects against high fructose and high sucrose induced liver damage[729]. Overall, **glycine is one of the best 'antidotes' to excess fructose/sugar intake**[730].

To sum up, preventing cardiovascular disease may boil down to having strong and healthy capillaries, which means

optimal intakes of hydrolyzed collagen, glycine, vitamin C, copper, and vitamin A.

Chapter 6: Collagen and Glycine for the Brain

Collagen has many benefits in terms of supporting brain health. **Supplementing with 5 grams of hydrolyzed collagen for 4 weeks in healthy adults improves cognitive function (learning and memory) and measures of brain structure**[731]. Ingestion of hydrolyzed collagen may help in the recovery from brain injury by promoting angiogenesis or the formation of new blood vessels[732] and exerting neuroprotective effects via suppressing inflammation[733]. Animal

studies also support the benefits of collagen for improving learning and memory[734]. Collagen VI protects the brain against beta-amyloid proteins, which are implicated in Alzheimer's disease[735]. Thus, collagen has great potential for protecting the central nervous system and it may even help heal injured brain cells. In this chapter, we're going to look at the effects of collagen and glycine on the brain.

Collagen as a Novel Delivery Method for Therapeutics Targeting Central Nervous System Regeneration

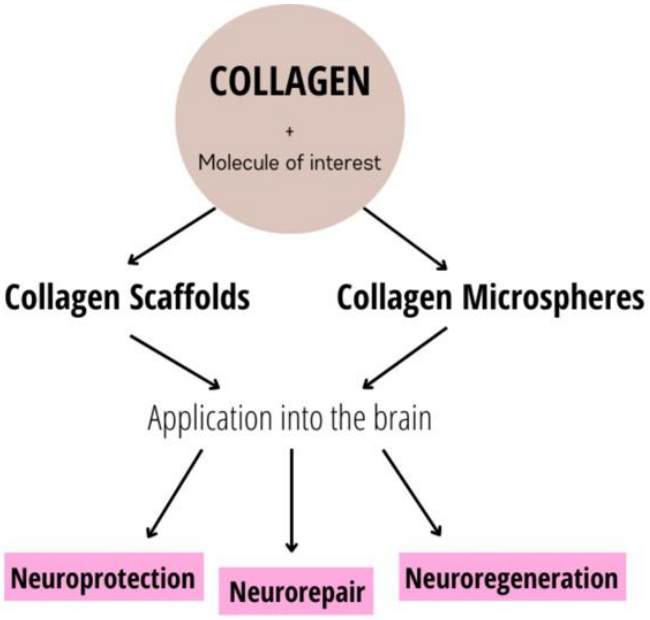
The central nervous system (CNS) has a very low ability for regeneration[736]. Biomaterials like collagen can now provide new avenues for protecting and regenerating the CNS[737],[738]. Loading collagen scaffolds with therapeutic agents can yield numerous benefits[739], [740],[741]. The advantage of this method over a systemic approach is localized delivery and minimized side effects[742].

Extracellular matrix (ECM) proteins have a key role in cell differentiation, attachment, survival, migration, and replication[743]. They can interact with cells directly through cell surface receptors as well as indirectly via other ECM molecules, which gives them the advantage in tissue repair. Some examples of natural ECM proteins include collagen I, alginate, chitosan, and gelatin. Collagen IV is the most abundant ECM protein in the basal membrane of the vasculature[744]. Research suggests there is decreased vascular density in aging and neurodegeneration[745].

Collagen is a hydrogel, which has the capacity to store a lot of water molecules, making it one of the primary compounds of interest for CNS repair because you can place it into soft nervous tissue[746],[747]. Collagen can also be processed into different forms, such as films, shields, sponges, and nanoparticles[748],[749].

Collagen scaffoldings (CollScaff) are easily produced and can be loaded with therapeutics that reach the brain[750]. They can contain nerve growth factor (NGF) or vascular endothelial growth factor (VEGF)[751],[752]. The bioavailability of most conventional drugs

and supplements is restricted due to the blood-brain-barrier (BBB) and they degrade before reaching their target[753]. CollScaff encapsulation prevents them from degrading prematurely.



Adapted From: Ucar and Humpel (2018)

As of now, collagen is used extensively in FDA-approved nerve conduits and cuffs (NeuraGen®, NeuroFlex®,

NeuroMend®, NeuroWrap® and NeuroMend®), which support nerve regeneration over nerve gaps up to 2-3 centimeters in peripheral nervous system injuries[754],[755]. BDNF-loaded injectable agarose gel supports axon growth and reduces inflammation in spinal cord injury[756]. However, collagen can be superior in this area, as it can form a gel at body temperature, making it more stable[757]. Collagen microspheres are also able to deliver growth factors to the brain in a safe and efficient manner to promote neuro-regeneration as well as regenerate spinal cord lesions[758].

Collagen scaffolds and other ECM proteins as carriers for therapeutic agents is still a relatively novel and inaccessible treatment for many people. However, it does reveal the diverse potential of collagen as a compound in terms of health and anti-aging. Fortunately, besides these biomaterial encapsulations, collagen and glycine as conventional supplements have a positive impact on brain function and regeneration.

Glycine in Brain Function

A lot of the neuroprotective effects of collagen are derived from glycine[759], [760],[761],[762]. Glycine blocks the formation of reactive oxygen species (ROS) in brain mitochondria and promotes survival of neuronal stem cells[763],[764]. In the rat brain, glycine inhibits ethanol-induced oxidative stress, neuroinflammation and neurodegeneration[765],[766]. Glycine also helps to reduce brain damage in rats caused by hypoxia/ischemia[767].

As a neurotransmitter, **glycine has two major roles: (1) in the spinal cord and**

brainstem, it exerts beneficial effects through the potentiation of GABA signaling, and (2) throughout the central nervous system, glycine also acts as a co-agonist together with L-glutamate at N-methyl-D-aspartate receptors (NMDARs)[768],[769],[770]. This means glycine will bind to glycine receptors and activate them to elicit benefits, such as enhanced seizure threshold[771], neurogenesis and neuroprotection. Impaired glycine receptor function is linked to neurological diseases and increased neuronal damage[772],[773]. Glycine receptors control the generation of neurons in the

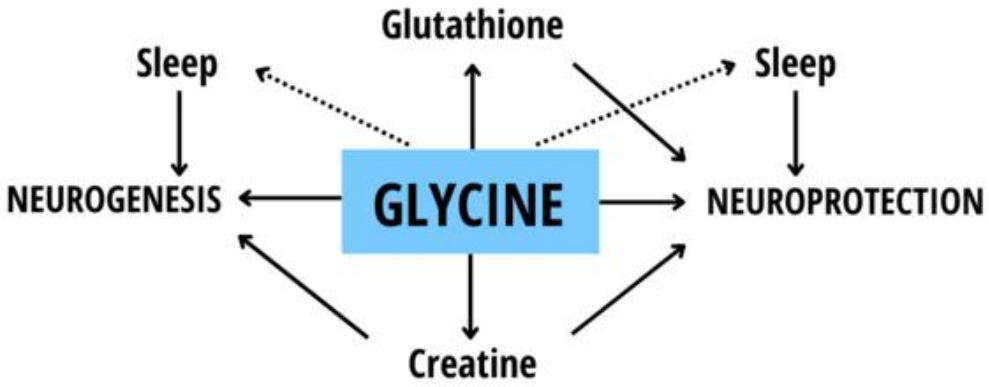
cerebral cortex[774]. You also need working glycine receptors for the formation of cerebral cortical circuits[775]. In the hippocampus, glycine N-methyltransferase supports neurogenesis, or the growth of new brain cells, and cognitive function[776]. It is no wonder then that **glycine has been found to be beneficial for memory**[777], [778]. There's a significant amount of glycine in the human brain, in white and gray matter, wherein executive function is processed[779]. BDNF or brain-derived neurotrophic factor, also known as the fertilizer for the brain[780], regulates

glycine uptake in hippocampal synaptosomes by reducing glycine transporter 2[781]. By increasing BDNF with things like exercise, intermittent fasting and deep sleep, you can activate glycine transporter 2 in the brain, helping with its neuroprotective and neuro-growth effects[782],[783],[784],[785],[786],[787].

Glycine is primarily an inhibitory amino acid similar to GABA (gamma-aminobutyric acid) – the main inhibitory neurotransmitter in the brain[788],[789],[790],[791]. Oral supplementation of glycine raises serotonin, the relaxation neurotransmitter[792], which is why

glycine has been shown to improve sleep quality[793],[794]. Serotonin gets converted into melatonin, which helps with falling asleep[795]. Melatonin helps with contrast sensitivity, or the ability to detect minor differences in luminance between a target and its surroundings in the darkness, which is largely mediated by glycinergic amacrine cells in the inner retina[796],[797]. Having better contrast sensitivity also translates into better face recognition, mobility, and driving[798]. Even cannabinoid-induced analgesia is mediated by glycine receptors[799]. **Glycine can also help to overcome fatigue and tiredness caused by sleep**

deprivation[800]. So, if you only get 6 hours of sleep instead of 8 hours, glycine can bring you back to baseline in terms of your energy levels and brain performance. It's no coincidence that creatine can do the same[801],[802], and as we know, glycine helps with creatine synthesis. Creatine has also been shown to prevent the decrease of hippocampal neurogenesis caused by stress[803]. The synthesis of creatine is a tremendous methylation burden[804], which is needed for overall health. Preventing imbalanced methylation could reduce the risk of cancer and heart disease[805],[806],[807].



Because of its inhibitory effects, glycine can help with excitatory conditions, such as obsessive-compulsive disorder (OCD) [808]. Over the course of 5 years, **glycine treatment has been found to improve OCD, reduce OCD behavior, and improve cognition**[809]. In rats, the glycine reuptake inhibitor Org24598 reduces ethanol intake[810]. This suggests that **keeping extracellular glycine levels elevated in the brain**

may reduce alcohol addiction[811]. In other animals, glycine reuptake inhibitors, which keeps brain glycine levels elevated, are helpful in drug addiction and cocaine-seeking behavior[812]. Thus, glycine can be a safe and easy supplement for such obsessive and addictive behavioral patterns. **Glycine also improves symptoms in schizophrenia and psychosis**[813],[814]. Mutations in the glycine cleavage system negatively affect symptoms of schizophrenia through metabolic changes[815]. Treatment with glycine has been found to improve negative, positive, and general symptoms in schizophrenia

and is well tolerated even at doses up to 60 grams per day[816].

You can activate glycine receptors (GlyR) with multiple compounds, but the biggest ones are glucose, taurine, beta-alanine and ivermectin[817]. The main precursor for GABA synthesis is glucose and a lot of the analgesic or sedative effects of glucose are mediated by glycinergic signaling[818],[819]. Activating glycine receptors with glucose isn't the best idea when done chronically, especially in pathological cases of insulin resistance or diabetes. However, **supplementing with taurine would be the most ideal and effective option** as

it works through activating glycine and GABA receptors[820],[821],[822]. Extracellular taurine inhibits neuronal firing through GABA and glycine receptors[823],[824]. Some additional compounds that can also activate glycine receptors are shilajit, zinc and blackcurrant anthocyanins[825],[826],[827],[828].

Here's how glycine helps the brain:

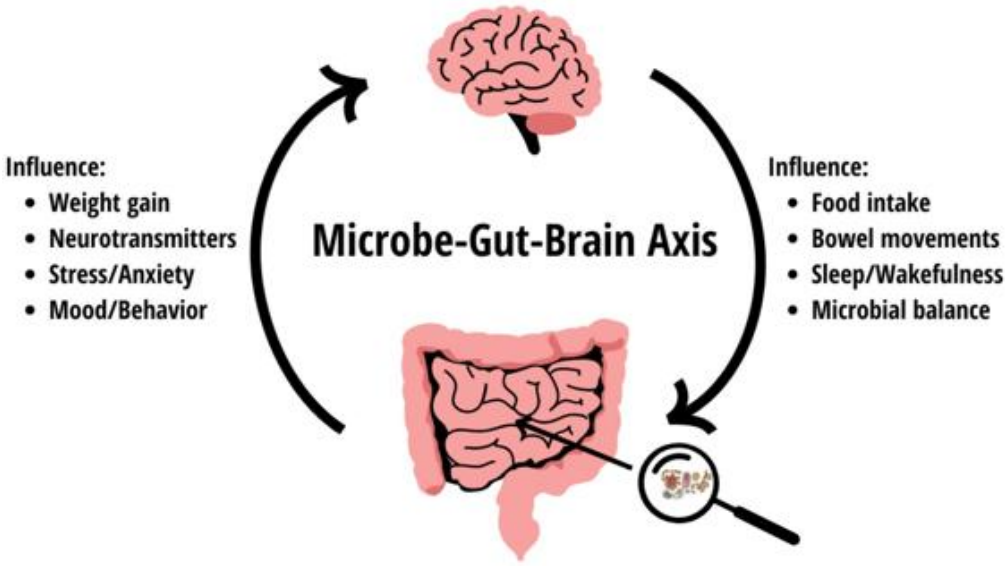
- Reduces oxidative stress
- Reduces neuroinflammation
- Provides neuroprotection through glutathione
- Increases GABA and inhibitory neurotransmission

- Helps with sleep and relaxation
- Promotes creatine synthesis
- Stimulates neurogenesis
- May reduce drug/ethanol seeking behavior

Gut-Brain Axis & Glycine

Science has revealed that our brain is connected to the microbiome in our gut, known as the Microbe-Gut-Brain (MGB) Axis[829]. The MGB Axis is a signaling network between the gastrointestinal tract (GI) and CNS[830]. It's even thought that the gut has a greater influential role on your state of mind and health than the brain[831]. **Systemic inflammation throughout the body is directly linked to the microbiome in the gut[832]. Shockingly, up to 70% of the immune system is in the gut, sending messages to the rest of the body[833].**

The microbiome helps to identify and differentiate pathogens and viruses, contributing to autoimmunity and adaptive immunity[834]. Thus, **your gut health determines your brain function and overall vitality.**



The brain is a very sensitive organ, which is why you don't want just anything to enter it. That's the function of the blood-brain barrier (BBB) – to separate

the bloodstream from the brain and let in only what's safe. A dysfunctional or permeable BBB can cause neuroinflammation, neuronal stress and other ailments[835], which usually originates from intestinal permeability. Also known as leaky gut, intestinal permeability is linked to autoimmunity and other inflammatory diseases[836], [837]. **To prevent intestinal permeability, you need to maintain the integrity of the tight junctions in the gut. Collagen peptides have been found to reduce intestinal epithelial barrier dysfunction via repair of the tight junctions**[838]. At the same time,

collagen-derived petides, such as glycine-prolyl-hydroxyproline and prolyl-hydroxyproline, are able to be fully absorbed into the body[839]. Glycine and prolyl-hydroxyproline are the primary reason for gelatin's anti-colitis effects and taking them as free compounds have better efficacy than when ingested as part of gelatin[840].

Glycine has a positive impact on gut health and inhibits oxidative stress, reducing inflammation and decreasing intestinal injury during endotoxemia[841],[842],[843],[844],[845],[846].

The glycine transporter GLYT1 is essential for the protection of intestinal

epithelial cells by glycine[847],[848]. **Glycine** beneficially affects the function of the intestinal mucosa[849],[850] as it **can improve mucosal regeneration**[851]. **Supplementing with glycine also improves intestinal integrity**[852]. Both glycine and L-arginine supplementation can repair colonic wall damage, but glycine has a superior effect to L-arginine[853]. However, **both L-arginine and glycine are effective against acid reflux esophagitis**[854]. Glycine alone, but particularly when combined with glucose, improves diarrhea and hydration status in cholera patients[855]. It

seems glycine at smaller and more frequent doses is better absorbed and causes fewer side-effects like nausea[856].

Next to collagen and glycine, a common supplement for supporting intestinal health and decreasing gut permeability is glutamine[857]. **Glutamine** is the main fuel for cells of the intestine and it **may help to protect against leaky gut**[858]. Glutamine may even help with food sensitivities by reducing inflammation on the gut surface[859]. In the immune system, glutamine supports lymphocyte proliferation and immune cell function[860],[861].

Ways to improve permeability of the gut and BBB:

- Prebiotics and dietary fiber[862]
- Limit refined grains[863]. People with celiac disease have higher serum zonulin levels[864].
- Do some intermittent fasting[865]. Ghrelin, the hunger hormone, has been shown to prevent BBB dysfunction after traumatic brain injury[866].
- Exercise regularly[867]
- Get enough REM sleep[868]. Sleep deprivation impairs BBB integrity[869].

- Limit alcohol[870]
- A diet high in vegetables, meat and fish benefits the microbiome[871]
- Limit the use of antibiotics

Your brain and gut are in many ways your two most valuable organs. Supporting both with optimal intakes of collagen, glycine, glutamine, and taurine are easy and effective strategies.

Here are the optimal daily doses for collagen, glycine, glutamine, and taurine:

- Collagen: 10-20 grams (divided into two daily doses)
- Glycine: 10-15 grams (divided into three daily doses)

- Glutamine: 6-15 grams (divided into three daily doses)
- Taurine: 1-3 grams (divided into two daily doses)

Chapter 7: Exercise and Collagen Health

Exercise is a major contributor to improved bone mineral density and overall health[872]. There's a lot of evidence showing that regular physical activity, especially resistance training, is protective against developing osteoporosis later in life as well as helping with its symptoms[873],[874],[875],[876]. Even 16 weeks of weight-bearing exercise is enough to increase bone mineral density in elderly women[877]. **Physical activity and exercise impose**

mild stress to the bones, which activates cells that build bone (osteoblasts)[878]. Hormones like testosterone, estrogen, and insulin-like growth factor 1 (IGF-1) also affect this process[879],[880],[881],[882],[883],. The reason post-menopausal women have a higher risk of osteoporosis is because of the decline in estrogen's protective effects on the joints and collagen synthesis[884],[885]. **Oral contraceptives inhibit collagen synthesis**[886],[887]. Low testosterone and IGF-1 levels are also associated with sarcopenia (muscle loss) [888],[889],[890],[891]. There is also an association between higher levels of

IGF-1 and reduced skin wrinkling[892]. In this chapter, we're going to focus on how exercise affects collagen synthesis and overall bone/tendon health.

Exercise and Collagen Synthesis

Physical impact on the joints caused by exercise triggers a cascade of events that strengthens the bones and increases their density. Taking collagen peptides after resistance training enhances collagen synthesis, improves body composition (decreased fat mass and increased fat-free mass) and increases muscle strength in elderly men compared to resistance training alone[893]. Taking vitamin C-enriched gelatin before intermittent activity promotes more collagen synthesis than not taking anything at all[894]. **The**

studies show that you will synthesize twice as much collagen when consuming 15 grams of gelatin with 48 mg of vitamin C 1 hour prior to exercise vs. not doing so. Thus, we recommended consuming collagen or gelatin within 1 hour of exercise as the amino acids peak at 1 hour[895]. Adding vitamin C to that can have an additional benefit. The increased blood flow to tendons/ligaments during exercise makes it an ideal time to supplement with collagen. The increased blood flow will help drive the collagen peptides where they need to go. Thus, while most people take their collagen powders in the morning with their cup of coffee, taking

collagen within an hour of exercise is more optimal.

Supplementing with collagen hydrolysate increases the proteoglycan content in knee cartilage[896]. This suggests that taking hydrolyzed collagen may help to reduce the risk of osteoarthritis. Indeed, gelatin/collagen peptides get distributed into joints after oral intake[897], where these peptides can stimulate cartilage cells to produce type II collagen and proteoglycans[898]. Studies in mice have even shown that hydrolyzed collagen reduces the progression of osteoarthritic lesions[899].

High load resistance training (3 sets of 8 reps at 70% of 1 rep max, 3-times per week) yields a greater increase in bone mineral density of the spine compared to moderate load resistance training (3 sets of 10-13 reps at 40-60% of 1 rep max, 3-times per week)[900]. For better testosterone and IGF-1 responses, heavier resistance training (5 reps at 80-90% of 1 rep max with 1-3 min rest) or moderate resistance training (10 reps at 75% of 1 rep max with 1 min rest) is needed, whereas moderate intensity long rest exercise (10 reps with 3 min rest) is not optimal for testosterone and IGF-1 responses[901],[902]. Heavier loads with

longer rest periods between sets (3 minutes instead of 1 minute) promote a longer elevation of testosterone[903]. For muscle growth, heavier weights (5 reps at 80-90% of 1 rep max with 1-3 min rest) also appears to be superior for strength and hypertrophy compared to moderate heavy weights (10 reps at 75% of 1 rep max with 1 min rest)[904],[905]. However, this doesn't mean that heavier weights are always a better option for everyone. In many cases, the average person would still benefit from 5-6 reps at 75-80% of 1 rep max versus 10 reps; especially if you're a beginner. Strength and muscle hypertrophy can even occur

at 40% of your 1 rep max if each set is performed close to failure, whereby the last 2-3 reps are difficult. For a more thorough overview of training, muscle hypertrophy and muscle strength, check out our book WIN: Achieve Peak Athletic Performance, Optimize Recovery and Become a Champion.

In humans, as few as 10 maximum vertical jumps a day for 3 days a week is enough to increase bone mineral density in young women[906]. Longer **rest intervals between exercise sets (30 seconds) have a more powerful anabolic effect on the bone than shorter rest intervals (3 seconds)[907].**

This suggests that tendons, ligaments, and bone get the most stimulus for collagen synthesis when you perform near maximum intensity activity for a short period of time combined with longer rest periods. Any exercise that increases blood flow to tendons/ligaments will help stimulate collagen production, some examples include, 40-yard dash, Olympic weightlifting, powerlifting, strength training, plyometrics such as box jumps, jumping rope and kettlebell exercises. Uphill running and skiing do the same[908],[909].

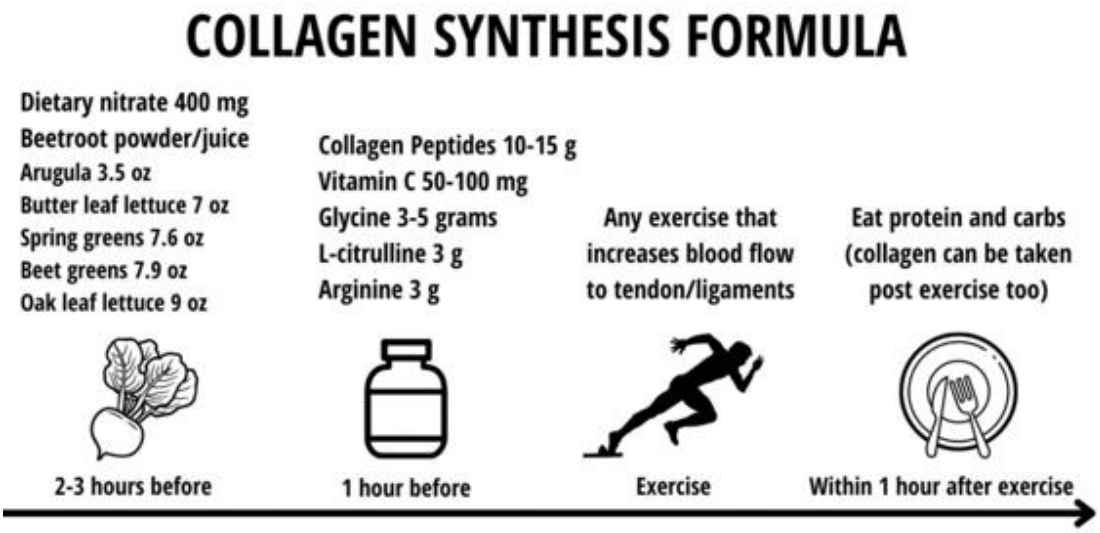
Exercise and especially resistance training, increase both growth hormone

(GH) and IGF-1[910],[911]. Combined sprint and resistance training reduces the age-related decline in growth hormone and IGF-1 levels[912],[913]. **GH and IGF-1 can stimulate cartilage synthesis and increase bone density and collagen synthesis**[914],[915],[916],[917],[918],[919],[920]**. GH stimulates collagen synthesis without affecting muscle fiber protein synthesis**[921]**. The increase in GH and IGF-1 levels precedes the increase in procollagen expression and collagen synthesis**[922],[923]**.** A long period of high mechanical stress on tendons and ligaments can lead to degeneration if appropriate collagen supplementation

does not occur. In hindsight, the combination of lifting heavy weights for a decade, in conjunction with no collagen supplementation, is likely why Dr. DiNicolantonio tore his pectoralis tendon below his 1 rep max on bench press; the injury occurred when attempting a 5th rep at 205 pounds, which was around 80-85% of his 1 rep max[924].

Taking glycine and sodium before a workout can also help with exercise performance and potentially enhance collagen synthesis. Drinking high salt solutions before exercise has been shown to increase blood volume by up to 8%, increase exercise duration and

increase power output[925],[926],[927],[928]. Adding glycine to the solution improves sodium and water absorption. Glycine also reduces core body temperature and it may reduce muscle cramps[929],[930]. Taking supplemental L-citrulline/arginine (3 grams of each) and beetroot powder/juice (at least 400 mg of nitrate equivalents) can increase nitric oxide and blood flow to tissues. This would likely translate into greater delivery of collagen peptides into tendons/ligaments and better collagen synthesis/repair.

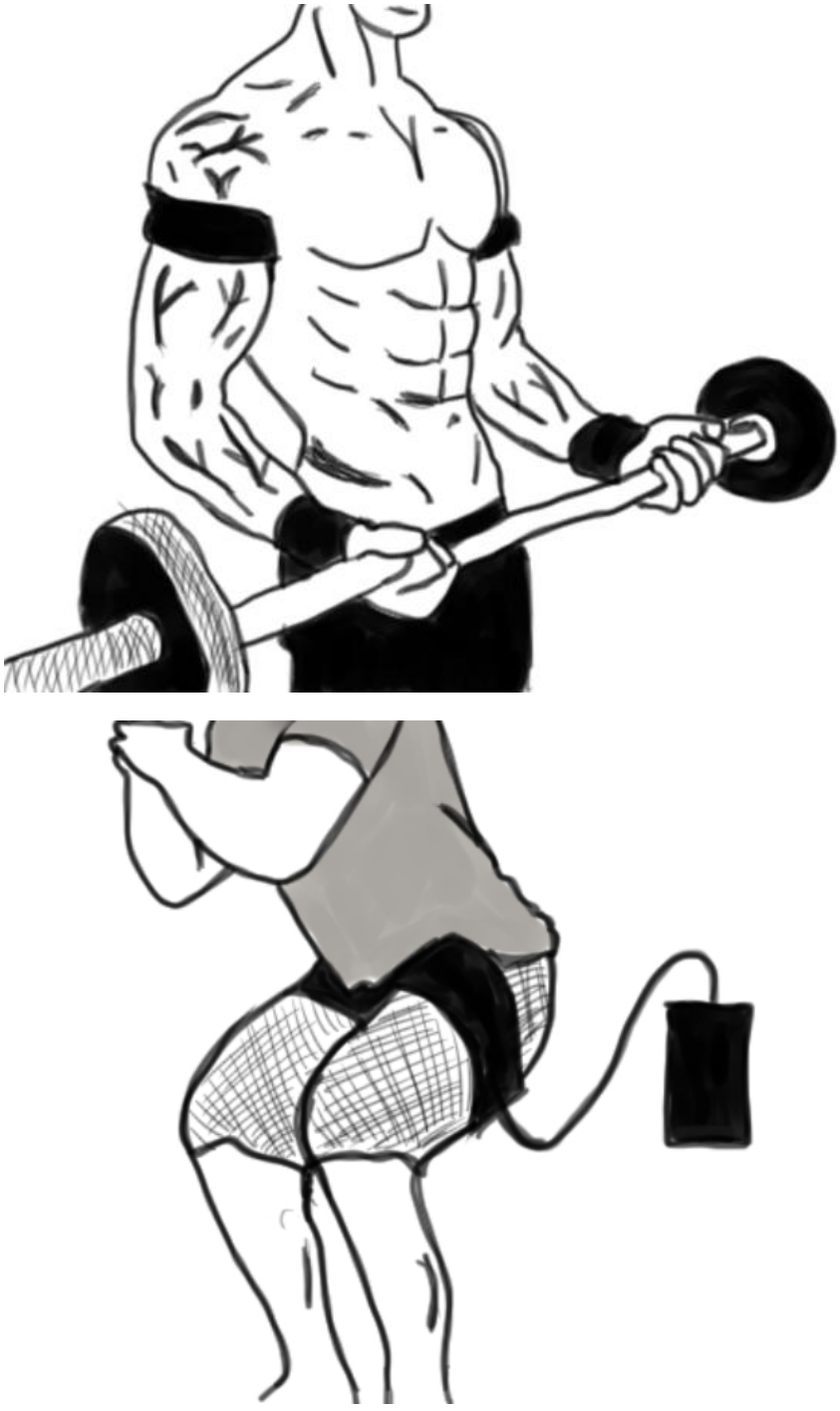

COLLAGEN SYNTHESIS FORMULA
Dietary nitrate 400 mg
Beetroot powder/juice
Arugula 3.5 oz
Butter leaf lettuce 7 oz
Spring greens 7.6 oz
Beet greens 7.9 oz
Oak leaf lettuce 9 oz
Collagen Peptides 10-15 g
Vitamin C 50-100 mg
Glycine 3-5 grams
L-citrulline 3 g
Arginine 3 g
Any exercise that increases blood flow to tendon/ligaments
Eat protein and carbs (collagen can be taken post exercise too)
2-3 hours before
1 hour before
Exercise
Within 1 hour after exercise

For Achilles tendon rupture healing, intermittent pneumatic compression upregulates collagen type I synthesis[931]. Intermittent pneumatic compression is a therapeutic technique that works by pumping air into inflatable sleeves on the arms or legs. It essentially pumps air in and out of the sleeves, making them deflate or inflate, which improves blood circulation in the given regions. This can be a preventive tool for

thrombosis, edema, or pulmonary embolism[932].

Similar effects can be seen with blood flow restriction (BFR) training. BFR restricts blood flow out of the muscles, making them pool up in the trained limb. As a result, greater oxidative stress is induced at a given weight, triggering more muscle growth and strength[933]. BFR training also helps with rehabilitation and function after Achilles tendon rupture[934]. When in traditional strength training, you need to train between 60-80% of your 1 rep max to build muscle and strength[935], whereas with BFR you can see these effects at

20-30% of your 1 rep max[936]. This is especially beneficial during injuries or for the elderly who can't exercise at maximum intensities. There are also multiple studies showing how BFR training prevents muscle atrophy and weakness in immobilized individuals[937], [938],[939],[940].



Blood flow restriction bands

BFR can enhance muscle protein synthesis without causing significant muscle damage[941],[942]. Blood flow restriction training is generally safe for all ages and genders[943]. Injuries are very rare but careless use may result in subcutaneous haemorrhage and numbness[944],[945]. A recent review found that the risk of venous thromboembolism is extremely low[946]. However, people with certain conditions, such as hypertension, history of stroke, cardiac disease, clotting disorders, pregnancy and vascular insufficiency should consult their physician first before using BFR.

Infrared Light and Collagen Synthesis

Exercise is a form of hormesis, which is a positive response to a moderate amount stress[947],[948]. In fact, many of the beneficial adaptations to exercise are mediated by the rise in inflammation and oxidative stress that it creates. **Interleukin-6 (IL-6) is an inflammatory cytokine that increases during exercise, and it stimulates collagen synthesis by increasing growth hormone[949].** On the other hand, taking antioxidants after exercise can blunt the

beneficial adaptations of exercise, especially muscle growth[950],[951].

Infrared light and red light are another beneficial hormetic stressor worth mentioning that **enhance collagen synthesis**[952],[953],[954],[955],[956]. Daily treatment with infrared light at 900-1000 nm for six months improves skin texture and tone[957]. **Use of red light therapy, also known as photobiomodulation, can reduce muscle pain, joint pain, soreness, arthritic pain and speed up wound healing**[958],[959],[960],[961],[962],[963],[964],[965],[966],[967],[968],[969],[970],[971],[972],[973],[974],[975]. Red/near infrared

(NIR) light stimulates cytochrome c oxidase in the mitochondrial electron transport chain, which increases ATP synthesis[976],[977],[978]. It also releases nitric oxide, rushing more blood flow to the muscles and tendons[979],[980],[981],[982].

Photobiomodulation was first used by a Niels Finsen, a physician from the Faroe Islands, who used it to treat various skin conditions, such as *lupus vulgaris* (a progressive form of tuberculosis) and smallpox lesions[983]. In 1903, Finsen won the Nobel Prize in Physiology or Medicine *'in recognition of his contribution to the treatment of diseases,*

especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science.'[984] Since the 1960s, laser therapy has been recognized to improve wound healing, pain, recovery and performance[985].

The benefits of photobiomodulation are dependent on certain wavelengths of light (specifically 630-900 nm and 900-1000 nm infrared light) with doses below that range not being beneficial[986]. Red light between 550-670 nm accelerates skin healing, whereas blue light between 430-510 nm slows it down[987]. Infrared wavelenghts

that you get exposed to in an infrared sauna begin at 900-1000 nm. If you do choose to try these devices out, then use them in moderation as they are still hormetic stressors. For red light therapy, around 5-10 minutes a day (at a distance of 30-60 cm) and 15-30 minutes per day for infrared sauna exposure seems optimal.

Collagen Cure Exercise Program

Here are some general exercise guidelines for optimal collagen and tendon health:

- Supplement with 10-20 grams of a Type I hydrolyzed collagen peptides
    - Also supplement with 1-2 grams of Type II hydrolyzed collagen (for cartilage health)
    - Consume with 50-100 mg of vitamin C within 1 hour of exercise
- Engage in resistance training at least 3x a week, incorporating free

weight exercises, such as squats, deadlifts, bench press and overhead press
    - Also include bodyweight exercises such as push-ups, pull-ups, dips, wall-ups and/or resistance machines/bands
- Aim for 6-12 reps where the last 2-3 reps are difficult with 1-3 minutes of rest between sets
- Try some maximum intensity exercises, such as all out sprints and vertical jumps but make sure to do an active warm up before high intensity exercises

What you don’t use, you’ll lose. That is especially true with your joints and

tendons as these tissues already suffer from not getting enough blood flow and growth factors. You need to provide them with the right nutrients and exercise stimulation to facilitate collagen synthesis in these regions. Both muscle tissue and collagen decrease with age, and both are incredibly valuable for longevity. It takes a long time to build muscle and bone density, but it's the most powerful antagonist against osteoporosis, sarcopenia, and frailty. Fortunately, it's well known that even acute resistance exercise increases protein synthesis in both young and older individuals[988]. A single bout of training can raise muscle

protein synthesis by 2-3 times[989]. Thus, it’s never too late to start exercising.

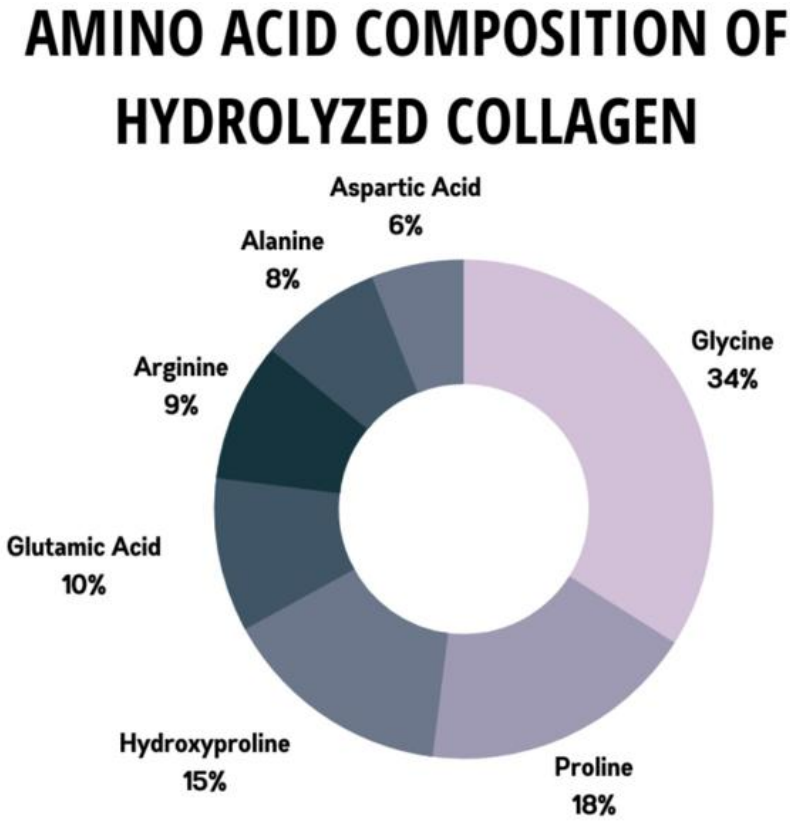
Chapter 8: The Full Collagen Cure Plan

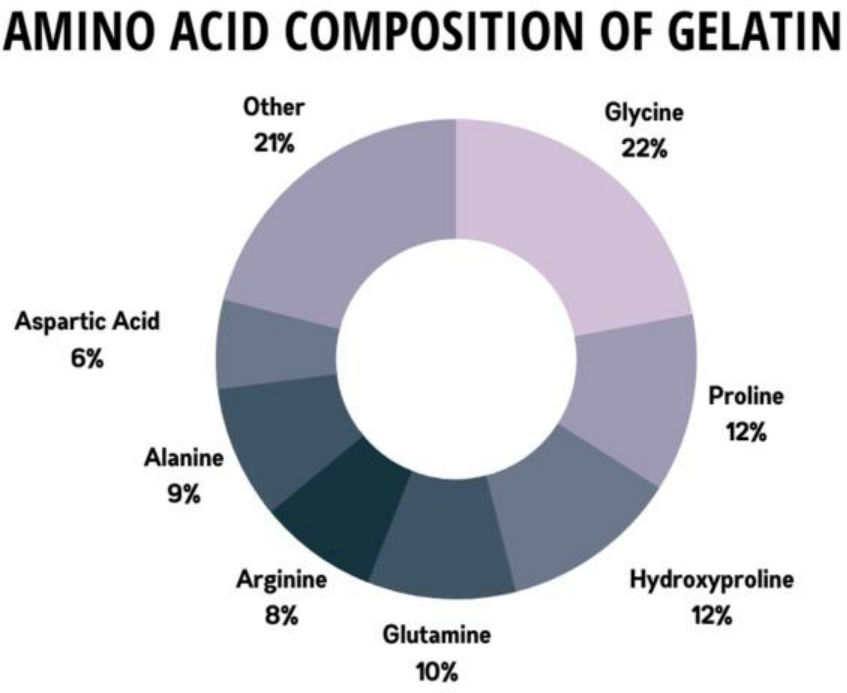
It’s time to get into a more specific protocol of incorporating collagen and glycine into our diets. The previous chapters have already shown you the main benefits of these compounds, but this chapter will cover the practical application in more detail. Let’s start with the two questions everyone wants to know – what foods have collagen and glycine and what foods support good collagen health.

Getting the Optimal Amount of Collagen and Glycine

Collagen and gelatin are comprised of multiple amino acids, primarily glycine (22-34%), hydroxyproline (7-15%) and proline (10-18%)[990],[991]. Additionally, they contain alanine (8-11%), arginine (8-9%), aspartic acid (6-7%) and glutamic acid (10-12%). Generally, **collagen-rich foods are the bones, cartilage, and gelatinous parts of animal protein, such as fish skin, fish bones, poultry skin, poultry bones, beef bones, tendons, ribs, etc.** Gelatin is a cooked form of collagen that's slightly different, although with a very similar amino acid

profile[992]. However, for optimal collagen synthesis you also need to be getting enough vitamin C, copper, iron, zinc, and other micronutrients.





Bone broth that forms this gelatin on top after refrigeration has precursors for collagen synthesis[993]. Unfortunately, the quantities of these in many bone broths are rather low making it an unreliable source of collagen[994]. However, making bone broth from animal bones/joints/tendons/skin etc. is a great way to get extra gelatinous amino acids

and not letting any part of the animal go to waste. Bone broth gelatin also has a similar amino acid profile as collagen with approximately 50% of it consisting of glycine, hydroxyproline and proline. Beef bones appear to have more amino acids than chicken bones[995]. Chicken soup has anti-inflammatory effects[996]. However, these effects vary greatly between commercial products, depending on the preparation method and quality of stock. Bone marrow is especially high in collagen. Cracking open the bones and eating the marrow is one theory of how hunter-gatherers developed bigger brains[997].

It takes about 8 hours of low simmer cooking to cook out 20% of the collagen in bones. Longer cooking times, even up to 72 hours, result in higher concentrations of amino acids in the broth. You can greatly increase this amount by breaking up the bones that you're about to cook. Cutting and breaking up bones helps the bone marrow and other nutrients come out during cooking. You can also buy marrow bones and cook them in a crock pot or an oven. Adding some vinegar may also help with the assimilation of the nutrients from the bones[998]. Overall, it is unlikely that bone broth alone would give you the optimal amount of 10-20 grams of

collagen a day, but it can certainly contribute to that amount.

The optimal amount of supplemental glycine per day is likely around 10-15 grams, but that number could be as high as 36 grams. However, 10 grams per day should cover optimal daily collagen turnover, whereas your endogenous synthesis of 3 grams/day will cover the synthesis of creatine, glutathione, heme, etc. If you take 10 grams of collagen peptides per day, you will be getting around 3 additional grams of glycine, which would cover the need for any endogenous synthesis of glycine in the formation of proteins and metabolites. If you eat some glycine-rich

foods you could easily get another 5 grams extra glycine, further increasing your glycine intake. However, if you don't eat a lot of skin, bones/bone marrow, tendons, etc. then taking a glycine supplement (3-5 grams, 3 times per day) can be worthwhile.

Here is an overview of the highest glycine foods[999],[1000]:

Food	**Amount of Glycine per 3.5 oz (100g)**
Pure Glycine Powder	100 g
Collagen	~30 g

Peptides Powder	
Dry Gelatin Powder	19.1 g
Gelatin Desserts	13.8 g
Pork Skin Snacks	11.9 g
Pork Ears	4.4 g
Whitefish	4.3 g
Soy Protein Isolate	3.6 g
Low-Fat Sesame Flour	3.4 g
Chicken	3.3 g

Skin	
Peanut Flour	3.1 g
Spirulina, Dried	3.0 g
Egg White Powder	3.0 g
Turkey Meat	3.0 g
Cod	3.0 g
Mollusks	2.9 g
Dried Egg Whites	2.8 g
Bacon	2.6 g
Lean Beef	2.2 g
Veal	2.2 g

Beef Sticks	2.1 g
Cuttlefish	2.0 g
Luncheon Meat	2.0 g
Lean Lamb	1.8 g

How to get an optimal intake of supplemental glycine/day:

- 3 grams in the morning
- 3 grams with lunch
- 10-15 grams of collagen peptides before or after exercise (providing 3-5 grams of glycine)
- 3 grams of glycine 1 hour before bed

Methionine depletes glycine levels and for every gram of methionine consumed your demand for glycine increases by 0.5-1 grams[1001]**.** A general rule is to consume an equal amount of protein in methionine-rich protein and glycine-rich protein or take a glycine supplement. Muscle meat and flesh is higher in methionine, whereas **glycine is found more in organ meats, tendons, ligaments, drumsticks, turkey necks and other collagenous meats**.

Here is an overview of the highest methionine foods[1002],[1003]**:**

Food	**Amount of**

	Glycine per 3.5 oz (100g)
Egg White Powder	3.2 g
Dried Egg Whites	2.8 g
Cod	1.8 g
Whitefish	1.7 g
Sesame Seed Flour	1.6 g
Whole Egg	1.5 g
Dried Spirulina	1.2 g
Mollusks	1.2 g

Lean Beef	1.1 g
Soy Protein Isolate	1.1 g
Brazil Nuts	1.1 g
Lean Lamb	1.1 g
Bacon	1.1 g
Parmesan Cheese	1.1 g
Pork	1.0 g
Beef Chuck	0.9 g
Chicken Breast	0.9 g

Ground Turkey	0.9 g
Mutton	0.9 g
Sturgeon	0.9 g
Beef Ribeye	0.9 g
Salmon	0.9 g
Tuna	0.9 g
Milk, Nonfat	0.9 g

Insufficient methionine intake could lower your IGF-1 levels, which contributes to osteoporosis and potentially increased risk of mortality[1004],[1005]**.** Both high, as well as low levels of IGF-1, are associated

with higher mortality[1006]. In fact, a meta-analysis of 12 studies with over 14,000 participants found that people with low IGF-1 were at a 1.27-fold higher risk of dying, whereas those with higher levels were at a 1.18-fold higher risk[1007]. Lower levels of IGF-1 may be more detrimental as you age. **Not getting enough methionine can also contribute to graying of hair**[1008]. That's obviously not what most people want. To prevent that, you still want to be eating proteins that have methionine – it's an essential amino acid that's involved in methylation[1009]. The main issue is the absence of glycine, as

glycine helps prevent the harms from excess methionine, such as homocysteine toxicity and accelerated aging.

Here are the foods that contain proline[1010],[1011]:

Food	**Amount of Proline per 3.5 oz (100g)**
Gelatin Powder	12 g
Gelatin Desserts	8.9 g
Pork Skin Snacks	7.0 g
Soy Protein	5.0 g

Isolate	
Parmesan Cheese	5.0 g
Goat Cheese	3.7 g
Milk, Nonfat	3.5 g
Buttermilk Milk	3.2 g
Egg White	3.2 g
Whitefish	3.0 g
Pork	2.9 g
Poppy Seeds	2.75 g
Mozzarella Cheese	2.75 g

Tofu	2.6 g
Sunflower Seed Flour	2.5 g
Spirulina, Dried	2.4 g
Mollusks	2.4 g
Soybeans	2.3 g
Beef, Cured	2.2 g
Turkey Skin	2.2 g
Cod	2.2 g

Here are the foods that contain hydroxyproline[1012],[1013]:

Food	**Amount of**

	Hydroxyproline per 3.5 oz (100g)
Turkey, Skin Only	0.9 g
Chicken Wing	0.7 g
Bacon	0.6 g
Turkey Gizzard	0.6 g
Ground Beef	0.6 g
Flaxseeds	0.6 g
Chicken Skin	0.6 g
Deer, Game	0.5 g

Pork Sausage	0.4 g
Fish	0.4 g
Ground Pork	0.3 g

Calcium and Bone Health

Lifelong physical activity, which includes weight-bearing exercise, adequate calcium intake and sufficient vitamin D levels reduce the risk of osteoporosis[1014],[1015]. Higher dietary calcium intake has been shown to increase bone mineral density with or without vitamin D[1016]. A 2015 meta-

analysis of 20 randomized controlled trials discovered that supplemental calcium could reduce the risk of fractures by 11%[1017]. Among 52,915 elderly adults in the U.S., calcium (500-1,200 mg/d) and vitamin D3 (300-1,000 IU/d) supplementation for up to 7 years decreased the risk of new fractures by 12%[1018]. The National Osteoporosis Foundation recommends a calcium intake of 1,000-1,200 mg/d and vitamin D 800-1,000 IU/d to middle-aged men and women[1019]. However, excessive calcium (>1,500 mg/d) decreases parathyroid hormone (PTH), which promotes low bone turnover[1020]. Too

much calcium can reduce the bone growth stimulating effects of PTH[1021]. The elderly, or someone with impaired calcium absorption, might need up to 2,400 mg/day of calcium but most adults only need around 1,000-1,200 mg/day.

Here are the highest calcium food sources[1022]

Food	**Mg of Calcium per Serving**	**% of RDA**
Yogurt, low fat, 8 oz	415 mg	32%
Orange Juice,	349 mg	27%

fortified, 1 cup		
Mozzarella, 1.5 oz	333 mg	26%
Sardines, canned, with bones, 3 oz	325 mg	25%
Cheddar Cheese, 1.5 oz	307 mg	24%
Milk, nonfat, 1 cup	299 mg	23%
Whole Milk, 1 cup	276 mg	21%

Yogurt, low fat, 6 oz	258 mg	20%
Tofu, firm, ½ cup	253 mg	19%
Salmon, 3 oz	181 mg	14%
Cottage Cheese, 1% fat, 1 cup	138 mg	11%
Tofu, soft, ½ cup	138 mg	11%
Fortified Cereal, 1 serving	130 mg	10%
Sardines,	110 mg	9%

without bones, 3 oz		
Frozen Yogurt, ½ cup	103 mg	8%
Turnip Greens, ½ cup	99 mg	8%
Kale, cooked, 1 cup	94 mg	7%
Ice Cream, ½ cup	84 mg	6%
Chia Seeds, 1 tbsp	76 mg	6%

Bok Choi, 1 cup	74 mg	6%
White Bread, 1 slice	73 mg	6%
Corn Tortilla, 6” diameter	46 mg	4%
Flour Tortilla, 6” diameter	32 mg	2%
Whole-Wheat Bread, 1 slice	30 mg	2%
Mussels, 3	28 mg	2%

oz		
Egg, whole, 1 medium	25 mg	2%
Kale, raw, 1 cup	24 mg	2%
Broccoli, raw, ½ cup	21 mg	2%
Cream Cheese, 1 tbsp	14 mg	1%
Liver, 3 oz	5.6 mg	0.5%

Collagen Supplements

Most people would benefit from increasing their daily collagen and glycine status with supplementation. However, the waters of collagen supplements are quite mirky. The most important thing to remember is that you want to be getting hydrolyzed collagen peptides, which are the ones that exert beneficial effects on skin aging, wrinkles, and joints[1023],[1024],[1025],[1026]. Typical daily dosages range from 5-20 grams.

Marine vs. Bovine Collagen

When it comes to collagen, the 2 main sources are bovine (cows) and marine

(fish). **Bovine collagen, sourced from cow hides and hooves, is mainly type I and III collagen, whereas marine collagen, sourced from scales and skins, is mainly type I.** Both have been shown to exert benefits, i.e., reduction in wrinkles, better skin elasticity and improved joint health[1027],[1028],[1029]. Bovine collagen has a higher amount of total amino acids, but fish collagen contains more hydroxyproline[1030],[1031]. Sharks and carp have the most hydroxyproline[1032]. Marine collagen peptides also have antioxidants that are effective in protecting the skin against UV radiation[1033],[1034].

Fish collagen peptides are smaller than bovine, which gives them superior bioavailability and digestibility[1035]. It's been found that marine collagen peptides are safe and effective in improving skin properties without any risk of oxidative damage[1036]. Marine collagen is an excellent source of collagen proteins because of its high bioavailability[1037]. Fish skin, bones, fins, heads, and bladders are "waste products" in fish food processing but they can be used to make high quality collagen. Up to 75% of the total weight of fish is discarded as waste[1038]. By reutilizing this unused

resource, we waste less food. Regardless, both bovine and fish collagen peptides are excellent and will have similar benefits.

Most hydrolyzed collagen supplements are from bovine hide composed mostly of Type I collagen and a little bit of Type III collagen. Bovine hide collagen is higher in glycine than gelatin because gelatin has less Type I collagen. Gelatin can be made from many things like joints, bones, cartilage, connective tissue, etc. This of course depends on how the gelatin is made because gelatin can either be the solidified product of bone broth or you can have gelatin from jello. Thus, there

are many different sources for different gelatins. **The biological effects of hydrolyzed collagen is greatly mediated by the two main peptides found in human blood after collagen consumption, prolyl-hydroxyproline (Pro-Hyp) and hydroxyprolyl-glycine (Hyp-Gly)**[1039],[1040]. Hyp-Gly may promote muscle growth via increased myoblast differentiation and myotube hypertrophy[1041]. It's been found that oral collagen-derived dipeptides, prolyl-hydroxyproline and hydroxyprolyl-glycine eliminate skin barrier dysfunction[1042]. Hydroxyprolyl-glycine and prolyl-hydroxyproline appear in the human

blood after ingestion of hydrolyzed collagen peptides[1043].

Eggshell Membrane Collagen

Eggshell membrane (ESM) is a supplement that helps support the joints and connective tissues[1044]. Supplemental ESM of 500 mg/day significantly reduces osteoarthritic joint pain and stiffness[1045],[1046],[1047],[1048],[1049]. Doses of 450 mg/day of hydrolyzed ESM for 12 weeks improves facial skin and hair appearance and wrinkles[1050],[1051],[1052]. Studies do find

that ESM supplements are safe for human consumption[1053].

Here's what you get from eggshell membrane[1054]:

- **Collagen** – the fibrous protein that supports your connective tissue
- **Elastin** – a protein that gives your skin and connective tissue its elasticity
- **Desmosine and isodesmosine** – two amino acids that give elastin its elastic properties
- **Glycosaminoglycans (GAGs)** – small quantities of glucosamine, chondroitin, and hyaluronic acid. They are essential polysaccharides needed for the structural integrity

of your connective tissue, extracellular matrix, and skeletal structure.

- **Transforming Growth Factor-B** - a protein that supports tissue rejuvenation, cellular differentiation, and immune function

Before you hastily start eating raw eggshell membranes for collagen, we caution you with the way you prepare and consume them. Eggshells can be a source of exposure to bacteria[1055]. You can get *Salmonella* from eggshells from chicken feces . **To avoid *Salmonella*, you should avoid eating eggshells and be careful with raw egg**

consumption. High temperatures wipe out *Salmonella*[1056], which is why you want to cook your eggshell membranes a bit before consumption. If you want to be extra cautious, you can even wash the eggshells with soap and water and then crack open the eggshell and peel the inner membrane off and throw it in a pan with your eggs to cook. Dr. DiNicolantonio has been consuming the inner white eggshell membranes on and off for several years. He has never washed the eggshells before cracking them open and peeling off the inner white eggshell membrane and hasn't had any issues. We don't recommend consuming the actual eggshells, but

some people will wash their eggshells with soap and water, let them dry out, and then use a coffee grinder to turn the eggshells into powder for additional calcium and nutrients. If someone doesn't eat vegetables or can't tolerate dairy, this might be a decent way to get calcium.

Vitamin C and Copper for Collagen Synthesis

To initiate collagen synthesis, you need vitamin C[1057]. Without it you won't be able to trigger the hydroxylation of proline and lysine, resulting in lack of collagen synthesis. Copper is required for the cross-linking of collagen via lysyl oxidase. On top of that, there are other micronutrients and minerals that either assist in collagen health or bone mineral density directly (such as manganese, zinc, iron, calcium, magnesium, and boron in particular).

Here are the highest sources of vitamin C from whole foods:[1058]

Food	Mg per serving
Red pepper, ½ cup	95
Orange juice, ¾ cup	93
Orange, 1 medium	70
Grapefruit juice, ¾ cup	70
Kiwifruit, 1 medium	64
Green pepper, ½	60

cup	
Broccoli, ½ cup	51
Strawberries, ½ cup	49
Brussels sprout	48
Tomato juice, ¾ cup	33
Cantaloupe, ½ cup	29
Cabbage, ½ cup	28
Potato, 1 medium	17
Tomato, 1	17

medium	
Spinach, ½ cup	9
Green peas, ½ cup	8

Here are the foods highest in copper[1059],[1060],[1061]:

Food	Mg of Copper per Serving	% of RDA minimum (0.9 mg-s)
Beef Liver, 3 oz	12.4 mg	1378%
Mollusks, 3	6.4 mg	600%

oz		
Oysters, 3 oz	4.8-6 mg	580%
Winged Beans, cooked, 1 cup	5.2 mg	530%
Lentils, cooked, 1 cup	2.5 mg	175%
Kidney Beans, 1 cup	2.0 mg	135%
Buckwheat, cooked, 1 cup	1.9 mg	130%

Seaweed, spirulina, 1 oz	1.7 mg	120%
Cocoa Powder, 1 oz	1.1 mg	110%
Pork, ham, 3 oz	0.8-1.1 mg	110%
Baking Chocolate, 1 oz	0.9 mg	104%
Beef Spleen, 3 oz	0.8 mg	90%
Spices, mace, 1 oz	0.7 mg	80%
Potatoes,	0.67 mg	75%

cooked, medium		
Thyme, 1 oz	0.67 mg	75%
Mushrooms, cooked, ½ cup	0.65 mg	72%
Cashew Nuts, 1 oz	0.62 mg	70%
Crab, cooked, 3 oz	0.62 mg	69%
Sunflower Seeds, ¼ cup	0.6 mg	68%
Black Pepper, 1 oz	0.59 mg	66%

Turkey, cooked, 3 oz	0.58 mg	65%
Dark Chocolate, 70-85%, 1 oz	0.5 mg	56%
Peanut Butter, 1 oz	0.5 mg	56%
Radishes, 1 oz	0.5 mg	56%
Game Meat, 3 oz	0.5 mg	56%
Pork Heart, 3 oz	0.5 mg	56%
Brazil Nuts, 1 oz	0.5 mg	56%

Tofu, firm, ½ cup	0.47 mg	53%
Beef Kidney, 3 oz	0.46 mg	50%
Beef Heart, 3 oz	0.45 mg	50%
Ham, 5% fat, 3 oz	0.45 mg	50%
Veal, cooked, 3 oz	0.45 mg	50%
Peanuts, oil-roasted, 1 oz (32 nuts)	0.4 mg	45%
Pecans, 1 oz (19 nuts)	0.3 mg	33%

Flaxseeds, 1 oz	0.3 mg	33%
Almonds, blanched, 1 oz	0.3 mg	33%
Chickpeas, ½ cup	0.29 mg	32%
Millet, cooked, 1 cup	0.28 mg	31%
Salmon, cooked, 3 oz	0.27 mg	30%
Whole Wheat Pasta,	0.26 mg	29%

cooked, 1 cup		
Turkey Breast, 3 oz	0.22 mg	28%
Chicken Breast, 3 oz	0.22 mg	28%
Beef Steak, 3 oz	0.1-2 mg	25%
Lamb, cooked, 3 oz	0.2 mg	24%
Pork, ribs, 3 oz	0.2 mg	24%
Avocado, ½ cup	0.2 mg	24%
Figs, dried,	0.2 mg	24%

½ cup		
Spices, curry powder, 1 oz	0.2 mg	24%
Spinach, cooked, ½ cup	0.15 mg	17%
Asparagus, cooked, ½ cup	0.14 mg	17%
Sesame Seeds, ¼ cup	0.14 mg	16%
Turkey, cooked, 3	0.13 mg	14%

oz		
Cream of Wheat, 1 cup	0.1 mg	12%
Gelatin, 1 oz	0.1 mg	12%
Egg, 1 medium	0.1 mg	12%
Fresh Garlic, 1 oz	0.1 mg	12%
Carrot, 1 oz	0.1 mg	12%
Mussels, 3 oz	0.1 mg	12%
Sardines, 3 oz	0.1 mg	12%
Tomatoes, raw, ½ cup	0.05 mg	6%

Greek Yogurt, 7 oz	0.042 mg	5%
Milk, no fat, 1 cup	0.027 mg	3%
Apples, raw, ½ cup	0.017 mg	2%

Zinc for Skin and Bones

Another mineral that we haven't talked about too much is zinc. Zinc is involved in wound healing[1062],[1063],[1064],[1065]. Zinc sulfide nanoparticles improve skin regeneration[1066]. A deficiency in zinc slows down tissue regeneration, whereas giving zinc normalizes this process[1067]. Foot ulcers are exacerbated without zinc and oral zinc sulfate supplementation improves foot and leg ulcers[1068],[1069],[1070],[1071],[1072]. Zinc helps to promote calcification of bone and collagen synthesis[1073],[1074],[1075].

However, zinc is a copper antagonist and large doses of zinc can cause copper deficiency by inhibiting its absorption. A high zinc concentration in the small intestine releases metallothionines, which bind to copper[1076]. In fact, zinc supplementation might be a leading cause of subclinical copper deficiency[1077]. Supplementing zinc at 50 mg/day can reduce copper status[1078],[1079]. However, it is unlikely that short term intakes of 40-50 mg of zinc per day will cause copper deficiency if the daily copper intake is above 1 mg/day. **The golden rule to remember,**

is that when you're supplementing with zinc, you want to get 1-2 extra milligrams of copper for every 40 mg of zinc.

Here are the foods highest in zinc[1080],[1081],[1082]

Food	Mg of Zinc per Serving	% of RDA minimum (11 mg)
Mollusks, 3 oz	154 mg	1029%
Oysters, 3 oz	74 mg	673%
Beef, chuck roast, 3 oz	7 mg	64%

Crab, cooked, 3 oz	6.5 mg	59%
Ground Beef, 80/20, 3 oz	5.4 mg	49%
Beef Patty, 3 oz	5.3 mg	48%
Wheat Germ, ¼ cup	4.8 mg	44%
Beef Liver, 3 oz	4.5 mg	41%
Buckwheat, cooked, 1 cup	4.1 mg	27%

Peanut Butter, 1 oz	4.0 mg	26%
Lamb, cooked, 3 oz	4.0 mg	26%
Beef Steak, 3 oz	4.0 mg	26%
Lobster, cooked, 3 oz	3.4 mg	31%
Pork Chop, cooked, 3 oz	2.9 mg	26%
Baked Beans, ½ cup	2.9 mg	26%

Breakfast Cereal, fortified with zinc, 1 serving	2.8 mg	25%
Lentils, cooked, 1 cup	2.5 mg	24%
Chicken, cooked, 3 oz	2.4 mg	22%
Mussels, 3 oz	2.3 mg	22%
Pumpkin Seeds, 1 oz	2.2-4.4 mg	20%
Cocoa	1.9 mg	13%

Powder, 1 oz		
Peanuts, oil-roasted, 1 oz (32 nuts)	1.9 mg	13%
Yogurt, low fat, 8 oz	1.7 mg	15%
Cashews, roasted, 1 oz	1.6 mg	15%
Chickpeas, cooked, ½ cup	1.3 mg	12%
Pecans, 1 oz (19 nuts)	1.3 mg	12%

Swiss Cheese, 1 oz	1.2 mg	11%
Flaxseeds, 1 oz	1.2 mg	11%
Sardines, 3 oz	1.2 mg	11%
Oatmeal, instant, 1 packet	1.1 mg	10%
Milk, low fat, 1 cup	1.0 mg	9%
Hemp Seeds, 1 tbsp	1.0 mg	9%
Baking	1.0 mg	9%

Chocolate, 1 oz		
Almonds, roasted, 1 oz	0.9 mg	8%
Brazil Nuts, 1 oz	0.9 mg	8%
Kidney Beans, cooked, ½ cup	0.9 mg	8%
Cheddar Cheese, 1 oz	0.9 mg	8%
Dark Chocolate,	0.9 mg	8%

70-85%, 1 oz		
Mushrooms, cooked, ½ cup	0.7 mg	5%
Salmon, cooked, 3 oz	0.7 mg	5%
Seaweed, spirulina, 1 oz	0.6 mg	4%
Spices, mace, 1 oz	0.6 mg	4%
Egg, 1 medium	0.6 mg	4%
Green Peas, ½ cup	0.5 mg	4%

Boron for Strong Bones

Boron is the forgotten mineral for optimal bone health. Boron is not considered an essential mineral and it has no established recommended daily allowance (RDA). However, boron has many anti-inflammatory and anti-osteoporotic effects[1083],[1084],[1085],[1086]. In areas where boron intakes are less than 1.0 mg/day, the estimated rates of osteoarthritis range from 20-70%, whereas in regions with intakes of 3-10 mg/day, the rates for arthritis are 0-10% [1087]. **In a small pilot study, 6 mg of boron per day for 8 weeks reduced osteoarthritis symptoms in 50% of the**

participants compared to 10% in the placebo group[1088]. Boron also increases vitamin D3 levels[1089],[1090]. Taking 3 mg/day of boron after 63 days of boron deprivation raises 25-OH-vitamin D (calcidiol) levels in older men and women[1091].

Boron doesn't have an established RDA, but the World Health Organization says an acceptable safe range of boron intake is 1-13 mg per day for adults[1092],[1093]. A high boron diet is considered to be 3.25 mg per 2,000 calories[1094]. An optimal intake of boron per day is around 3 mg. Prunes (dried plums) are the

highest source of boron, providing 1.5 to 3.0 mg of boron per 3 oz serving[1095].

Here are the top boron-containing foods[1096],[1097],[1098],[1099]

Food	Mg of Boron per Serving	% of 3 mg/d
Prunes (dried plum), 1 cup	7.2 mg	240%
Red Kidney Beans, 1 cup	2.48 mg	83%
Avocado, 1	2.06 mg	68%

cup		
Black Currants, 1 cup	1.74 mg	58%
Lentils, 1 cup	1.47 mg	49%
Prune Juice, 1 cup	1.43 mg	47%
Raisins, 1 oz	1.28-1.40 mg	42-46.6%
Chickpeas, 1 cup	1.05 mg	35%
Plum, 1 cup (3.5 plums)	1 mg	33%
Peaches, 1 medium	0.80 mg	26%

Almonds, 1 oz	0.80 mg	26%
Hazelnuts, 1 oz	0.79 mg	26%
Dates, 1 oz	0.26 mg	11.5%
Grape Juice, 1 cup	0.76 mg	25%
Celery, 1 cup	0.75 mg	25%
Apples, 1 medium	0.66 mg	22%
Apricots, 1 oz	0.59 mg	19%
Red Wine, 5 oz glass	0.54 mg	18%
Pears, 1	0.50 mg	16%

medium		
Honey, 3 oz	0.50 mg	16%
Brazil Nuts, 1 oz	0.49 mg	16%
Peanuts, 1 oz	0.48 mg	16%
Broccoli, boiled, 1 cup	0.48 mg	16%
Walnuts, 1 oz	0.46 mg	15%
Apple Juice, 1 cup	0.45 mg	15%
Chili Con Carne	0.41 mg	13%

with Beans, 1 cup		
Grapes, ½ cup	0.37 mg	12%
Oranges, 1 medium	0.37 mg	12%
Lima Beans, cooked, ½ cup	0.35 mg	11%
Applesauce, ½ cup	0.34 mg	11%
Cashews, 1 oz	0.33 mg	11%
Orange Juice, 1 cup	0.18 mg	6%
Spinach,	0.16 mg	5%

cooked, ½ cup			
Banana, medium	**1**	0.16 mg	5%
Spaghetti Sauce, ½ cup		0.16 mg	5%
Carrots, medium	**1**	0.14 mg	4%
Peas, cooked, cup	**½**	0.10 mg	3%
Egg, medium	**1**	0.08 mg	3%
Coffee, cup	**1**	0.07 mg	2%

Lettuce, 1 cup	0.06 mg	2%
Tomatoes, ½ cup	0.06 mg	2%
Tuna, canned, 3 oz	0.05 mg	2%
Milk, whole, 1 cup	0.04 mg	1%
Corn, cooked, ½ cup	0.04 mg	1%
White Rice, cooked, ½ cup	0.03 mg	1%
Chicken	0.03 mg	1%

Breast, 3 oz		
Tea, 1 cup	0.02 mg	0.6%
Lamb, 3 oz	0.02 mg	0.6%
White Bread, 1 slice	0.01 mg	0.3%

To understand the incredible world of minerals and how to optimize them for your overall health, we highly recommend checking out our book The Mineral Fix.

Tips to Support Collagen Health

Here are some additional tips for supporting your collagen health:

) **Increase collagen production**

- Maintain adequate zinc, magnesium, manganese, sodium, and vitamin C intake.
- Exercise regularly, especially resistance training
- Infrared light exposure with either infrared saunas, red light therapy devices or natural sunlight to increase the production of collagen[1100],[1101],[1102]

) **Consume collagen, glycine, and eggshell membrane**

- Type I hydrolyzed collagen – Take 5-20 grams per day.
    - Try and find a grass-fed hydrolyzed collagen that tests for pesticides, herbicides, insecticides, heavy metals, etc. Ask the company for a certificate of analysis.
- Type II hydrolyzed collagen – Take 1-2 grams per day
- Undenatured Type II collagen – take 40 mg per day

- Multi-collagens – Certain multi-collagen supplements will have Type I, II, II and numerous other collagens contained within it. Taking these products can offer an advantage by getting many collagen types in one supplement.
- Glycine – Take 3-5 grams up to 3-times per day with each meal. Additionally, 3 grams of glycine an hour prior to bed can also help with sleep.
- Hydrolyzed eggshell membrane – Take 500 mg per day as a supplement.
    - Eating the inner membrane of eggshells after cooking it

may provide similar benefits.

- Consume the skin of foods– chicken skin, fish skin.
- Consume bone/collagenous broths [made from ham or beef hocks, drumsticks, turkey necks, etc.].
- Consume cooked bone marrow.

)**Get enough protein**

- Aim for 1-1.25 grams of protein per pound of lean (or target) bodyweight. Eat methionine-rich proteins but make sure you implement glycine supplementation.

) **Increase blood flow to the tendons/ligaments**

- This drives collagen peptides, amino acids, and vitamins/minerals where they need to go. You can try blood flow restriction training to magnify this process even further.
- Use a resistance band or perform resistance exercise within 1 hour of consuming glycine/collagen peptides.
- Incorporate high intensity free weight exercises as well as plyometrics to trigger bone density and collagen synthesis.

- Maintain good blood vessel health – Healthy carbs/fats/proteins, marine omega-3 intake (wild seafood or a quality fish oil), high potassium and magnesium intake (shellfish, fish, nuts, seeds, spinach, potatoes, beans, tomatoes, and dark chocolate)

) **Consume the vitamins/minerals that support collagen/elastin synthesis as well as collagen/elastin cross-linking**

- **Vitamin C** – cofactor for lysyl hydroxylase – bell peppers, citrus (strawberries, kiwi, mangos) and broccoli.

- **Copper** – cofactor for lysyl oxidase - liver, oysters, dark chocolate, seeds, mushrooms, nuts (pecans), raisins, avocado, sprouted whole grains. Sauna/sweating causes anywhere from 0.25-0.5 mg of copper loss per hour. Make sure to replace back the copper losses in sweat. Copper allows the body to use iron and it helps vitamin C get into the cell.
- **Vitamin A and retinol** improve skin thickness when applied topically[1103].
- **B vitamins** help to produce new skin cells and speed up wound

healing[1104],[1105]. Topical niacinamide also reduces skin pigmentation and aging spots[1106].

- **Avoid iron/zinc overload** – this can lead to copper deficiency. Make sure to eat some copper from liver, pecans, or dark chocolate instead of only eating muscle meat or fish.
- **Zinc, manganese, magnesium** – seafood, oysters, fish, pumpkin seeds, clams.
- **Selenium and iodine –** selenium and iodine deficiency can impair growth of bone and cartilage[1107].

Eat Brazil nuts, seafood, fish, sea vegetables.

) **Absorb and drive vitamin C into tissues**

- Requires sodium-dependent vitamin C transporters.
- Maintain adequate sodium status/intakes – Replace salt loss from low-carb diets, fasting, caffeine, exercise, and sauna therapy.

) **Avoid harmful breakdown of collagen (from oxidative stress/UV rays)**

- Consume high amounts of polyphenols, carotenoids, vitamin

E [grass-fed animal products] and vitamin C, glutathione precursors (glycine and cysteine).

- Be reasonable with direct sunlight exposure. Minimize sun exposure during midday. You don’t want to be vitamin D deficient, as vitamin D is important for bone density. An optimal vitamin D3 blood level seems to be between 40-80 ng/ml.
- Avoid refined grains, sugars, industrial seed oils, and processed foods in general (emulsifiers, phosphates, nitrates/nitrites, etc.).
- Fluoride induces programmed cell death and alters collagen I

expression[1108]. Avoid fluorinated water consumption.

- Get at least 7-8 hours of sleep per night.
- Limit advanced glycation end-product formation (avoid elevated levels of blood glucose by limiting the intake of refined sugars).

Factors That Affect Collagen Health

Mediator	Collagen Synthesis/Strength
Amino Acids	
Glycine	**+**
Hydroxyproline	**+**
Proline	**+**
Leucine	+

Glutamine	+
Methionine	+
Vitamins	
Vitamin C	+
Vitamin D	+
Vitamin A	+
B vitamins	+
Minerals	
Copper	+
Magnesium	+
Manganese	+
Zinc	+
Boron	+
Calcium	+
Exercise	
Resistance training	+
Blood flow	+

restriction training	
Plyometrics	+
Growth Factors	
PDGF (platelet-derived growth factor)	+
TGF-beta (transforming growth factor-beta)	+
FGF (fibroblast growth factor)	+
IGF (insulin-like growth factor)	+
Estrogen Estrogen boosters	+ Glycine/collagen (increases estrogen levels/mRNA), flavonoids

Testosterone Testosterone boosters	+ Resistance training, avoiding weight gain, proper sleep, moderate fat intake, carbohydrates
PGE_2	-
Matrix Metalloproteinases (MMPs)	-
MMPs inhibitors	+ Green tea, pomegranate, krill oil (astaxanthin), marine omega-3s
Glucocorticoids (cortisol, prednisone, methylprednisolone, inhaled steroids)	-

Processed Food	
Sugar	-
Refined carbohydrates	-
Omega-6 vegetable oils	-
High-fructose corn syrup	-
Fluoride	-

Conclusion

As you can see, collagen has an important role in aging as well as overall health. Countless studies have shown that supplementing with collagen and/or glycine has numerous health benefits. Additionally, these supplements work relatively fast and are without any real side-effects.

In the modern fitness community, collagen supplements are quite common, but the consumption of glycine and collagenous foods is less so. That's what we hope to change with this book. There are many components of the animals that are often discarded and wasted, but

they can provide us with valuable nutrition. The days of eating the skin on chicken and fish are essentially gone, but these are one of the most easily accessible sources of collagen in your diet. You should also incorporate optimal intake of all vitamins and minerals from a well-balanced diet. Lastly, daily exercise is important for any longevity routine because it triggers everything you want from optimal physical health to cognitive functioning. We wish you all the best on your journey of obtaining optimal collagen health.

References

[1] Statista (2021) 'Size of the anti-aging market worldwide from 2020 to 2026', Accessed Online: https://www.statista.com/statistics/509679/value-of-the-global-anti-aging-market/

[2] Deep Knowledge Analytics Limited (2021), 'Global Longevity Industry Investment Digest 2021/Q2', Accessed Online: https://www.einnews.com/pr_news/548413222/global-longevity-industry-investment-digest-2021-q2

[3] Precedence Research (2021) 'Collagen Market Size to Surpass Around USD 20 Billion by 2030', Accessed Online: https://www.globenewswire.com/en/news-release/2022/06/15/2463083/0/en/Collagen-Market-Size-to-Surpass-Around-USD-20-Billion-by-2030.html

[4] Clark, K. L., Sebastianelli, W., Flechsenhar, K. R., Aukermann, D. F., Meza, F., Millard, R. L., Deitch, J. R., Sherbondy, P. S., & Albert, A. (2008). 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. Current medical research and opinion, 24(5), 1485–1496. https://doi.org/10.1185/030079908x291967

[5] Elam, M. L., Johnson, S. A., Hooshmand, S., Feresin, R. G., Payton, M. E., Gu, J., & Arjmandi, B. H. (2015). A calcium-collagen chelate dietary supplement attenuates bone loss in postmenopausal women with osteopenia: a randomized controlled trial. Journal of medicinal food, 18(3), 324–331. https://doi.org/10.1089/jmf.2014.0100

[6] Sibilla and Borumand (2015) 'Effects of a nutritional supplement containing collagen peptides on skin elasticity, hydration and wrinkles', Journal of Medical Nutrition and Nutraceuticals 4(1):47.

[7] Choi, F. D., Sung, C. T., Juhasz, M. L., & Mesinkovsk, N. A. (2019). Oral Collagen Supplementation: A Systematic Review of Dermatological Applications. Journal of drugs in dermatology : JDD, 18(1), 9–16.

[8] DiNicolantonio and Fung (2019) ‘The Longevity Solution’. Victory Belt.

[9] Sayer, A. A., Syddall, H., Martin, H., Patel, H., Baylis, D., & Cooper, C. (2008). The developmental origins of sarcopenia. The journal of nutrition, health & aging, 12(7), 427–432. https://doi.org/10.1007/BF02982703

[10] Goodpaster, B. H., Park, S. W., Harris, T. B., Kritchevsky, S. B., Nevitt, M., Schwartz, A. V., Simonsick, E. M., Tylavsky, F. A., Visser, M., & Newman, A. B. (2006). The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. The journals of gerontology. Series A, Biological sciences and medical sciences, 61(10), 1059–1064. https://doi.org/10.1093/gerona/61.10.1059

[11] Goodpaster, B. H., Park, S. W., Harris, T. B., Kritchevsky, S. B., Nevitt, M., Schwartz, A. V., Simonsick, E. M., Tylavsky, F. A., Visser, M., & Newman, A. B. (2006). The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. The journals of gerontology. Series A, Biological sciences and medical sciences, 61(10), 1059–1064. https://doi.org/10.1093/gerona/61.10.1059

[12] Isoyama et al (2014) 'Comparative Associations of Muscle Mass and Muscle Strength with Mortality in Dialysis Patients', CJASN October 2014, 9 (10) 1720-1728; DOI: https://doi.org/10.2215/CJN.10261013

[13] Kraschnewski, JL. et al (2016) 'Is strength training associated with mortality benefits? A 15year cohort study of US older adults', Prev Med, Vol 87, p 121-127.

[14] Volaklis, KA. et al (2015) 'Muscular strength as a strong predictor of mortality: A narrative review', European Journal of

Internal Medicine, Vol 26(5), p 303-310.

[15] Kim, K., Park, S.M. Association of muscle mass and fat mass with insulin resistance and the prevalence of metabolic syndrome in Korean adults: a cross-sectional study. Sci Rep 8, 2703 (2018). https://doi.org/10.1038/s41598-018-21168-5

[16] Preethi Srikanthan, Arun S. Karlamangla, Relative Muscle Mass Is Inversely Associated with Insulin Resistance and Prediabetes. Findings from The Third National Health and Nutrition Examination Survey, The Journal of Clinical Endocrinology & Metabolism, Volume 96, Issue 9, 1 September 2011, Pages 2898–2903, https://doi.org/10.1210/jc.2011-0435

[17] Shorter, E., Sannicandro, A. J., Poulet, B., & Goljanek-Whysall, K. (2019). Skeletal Muscle Wasting and Its Relationship With Osteoarthritis: a Mini-Review of Mechanisms and Current Interventions. Current rheumatology reports, 21(8), 40. https://doi.org/10.1007/s11926-019-0839-4

[18] Hong, S., Chang, Y., Jung, H. S., Yun, K. E., Shin, H., & Ryu, S. (2017). Relative muscle mass and the risk of incident type 2 diabetes: A cohort study. PloS one, 12(11), e0188650. https://doi.org/10.1371/journal.pone.0188650

[19] Tyrovolas, S., Panagiotakos, D., Georgousopoulou, E., Chrysohoou, C., Tousoulis, D., Haro, J. M., & Pitsavos, C. (2019). Skeletal muscle mass in relation to 10 year cardiovascular disease incidence among middle aged and older adults: the ATTICA study. Journal of Epidemiology and Community Health, 74(1), 26–31. https://doi.org/10.1136/jech-2019-212268

[20] McClave et al (2001) 'Dissecting the energy needs of the body', Current Opinion in Clinical Nutrition and Metabolic Care: March 2001 - Volume 4 - Issue 2 - p 143-147.

[21] Nancy R Rodriguez, Introduction to Protein Summit 2.0: continued exploration of the impact of high-quality protein on optimal health, The American Journal of Clinical Nutrition, Volume 101, Issue

6, June 2015, Pages 1317S–1319S, https://doi.org/10.3945/ajcn.114.083980

[22] METTLER, S., MITCHELL, N., & TIPTON, K. D. (2010). Increased Protein Intake Reduces Lean Body Mass Loss during Weight Loss in Athletes. Medicine & Science in Sports & Exercise, 42(2), 326–337. doi:10.1249/mss.0b013e3181b2ef8e

[23] West, D. W., Burd, N. A., Coffey, V. G., Baker, S. K., Burke, L. M., Hawley, J. A., Moore, D. R., Stellingwerff, T., & Phillips, S. M. (2011). Rapid aminoacidemia enhances myofibrillar protein synthesis and anabolic intramuscular signaling responses after resistance exercise. The American journal of clinical nutrition, 94(3), 795–803. https://doi.org/10.3945/ajcn.111.013722

[24] Hasten, D. L., Pak-Loduca, J., Obert, K. A., & Yarasheski, K. E. (2000). Resistance exercise acutely increases MHC and mixed muscle protein synthesis rates in 78-84 and 23-32 yr olds. American journal of physiology. Endocrinology and metabolism, 278(4), E620–E626. https://doi.org/10.1152/ajpendo.2000.278.4.E620

[25] Longland, T. M., Oikawa, S. Y., Mitchell, C. J., Devries, M. C., & Phillips, S. M. (2016). Higher compared with lower dietary protein during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: a randomized trial. The American Journal of Clinical Nutrition, 103(3), 738–746. doi:10.3945/ajcn.115.119339

[26] Layman, D. K., Anthony, T. G., Rasmussen, B. B., Adams, S. H., Lynch, C. J., Brinkworth, G. D., & Davis, T. A. (2015). Defining meal requirements for protein to optimize metabolic roles of amino acids. The American journal of clinical nutrition, 101(6), 1330S–1338S. https://doi.org/10.3945/ajcn.114.084053

[27] Campbell, W. W., Trappe, T. A., Wolfe, R. R., & Evans, W. J. (2001). The recommended dietary allowance for protein may not be adequate for older people to maintain skeletal muscle. The journals of gerontology. Series A, Biological sciences and medical sciences, 56(6), M373–M380. https://doi.org/10.1093/gerona/56.6.m373

[28] Di Lullo, Gloria A.; Sweeney, Shawn M.; Körkkö, Jarmo; Ala-Kokko, Leena & San Antonio, James D. (2002). "Mapping the Ligand-binding Sites and Disease-associated Mutations on the Most Abundant Protein in the Human, Type I Collagen". J. Biol. Chem. 277 (6): 4223–31. doi:10.1074/jbc.M110709200

[29] Ricard-Blum S. (2011). The collagen family. Cold Spring Harbor perspectives in biology, 3(1), a004978. https://doi.org/10.1101/cshperspect.a004978

[30] Buehler M. J. (2006). Nature designs tough collagen: explaining the nanostructure of collagen fibrils. Proceedings of the National Academy of Sciences of the United States of America, 103(33), 12285–12290. https://doi.org/10.1073/pnas.0603216103

[31] Shuster, S., Black, M. M., & McVitie, E. (1975). The influence of age and sex on skin thickness, skin collagen and density. The British journal of dermatology, 93(6), 639–643. https://doi.org/10.1111/j.1365-2133.1975.tb05113.x

[32] Shuster, S., Black, M. M., & McVitie, E. (1975). The influence of age and sex on skin thickness, skin collagen and density. The British journal of dermatology, 93(6), 639–643. https://doi.org/10.1111/j.1365-2133.1975.tb05113.x

[33] Oliveira, S. M., Ringshia, R. A., Legeros, R. Z., Clark, E., Yost, M. J., Terracio, L., & Teixeira, C. C. (2010). An improved collagen scaffold for skeletal regeneration. Journal of biomedical materials research. Part A, 94(2), 371–379. https://doi.org/10.1002/jbm.a.32694

[34] Cunniffe, G.M., O'Brien, F.J. Collagen scaffolds for orthopedic regenerative medicine. JOM 63, 66–73 (2011). https://doi.org/10.1007/s11837-011-0061-y

[35] McCarty, M. F., O'Keefe, J. H., & DiNicolantonio, J. J. (2018). Dietary Glycine Is Rate-Limiting for Glutathione Synthesis and May Have Broad Potential for Health Protection. The Ochsner journal, 18(1), 81–87.

[36] Birbrair, A., Zhang, T., Files, D. C., Mannava, S., Smith, T., Wang, Z. M., Messi, M. L., Mintz, A., & Delbono, O. (2014). Type-1 pericytes accumulate after tissue injury and produce collagen in an organ-dependent manner. Stem cell research & therapy, 5(6), 122. https://doi.org/10.1186/scrt512

[37] Singh, O., Gupta, S. S., Soni, M., Moses, S., Shukla, S., & Mathur, R. K. (2011). Collagen dressing versus conventional dressings in burn and chronic wounds: a retrospective study. Journal of cutaneous and aesthetic surgery, 4(1), 12–16. https://doi.org/10.4103/0974-2077.79180

[38] Gould L. J. (2016). Topical Collagen-Based Biomaterials for Chronic Wounds: Rationale and Clinical Application. Advances in wound care, 5(1), 19–31. https://doi.org/10.1089/wound.2014.0595

[39] Garnero P. (2015). The Role of Collagen Organization on the Properties of Bone. Calcified tissue international, 97(3), 229–240. https://doi.org/10.1007/s00223-015-9996-2

[40] Hu, C. H., Yao, C. H., Chan, T. M., Huang, T. L., Sen, Y., Huang, C. Y., & Ho, C. Y. (2016). Effects of Different Concentrations of Collagenous Peptide from Fish Scales on Osteoblast Proliferation and Osteoclast Resorption. The Chinese journal of physiology, 59(4), 191–201. https://doi.org/10.4077/CJP.2016.BAE398

[41] Porfíro, E., and G. B. Fanaro. 2016. Collagen supplementation as a complementary therapy for the prevention and treatment of osteoporosis and osteoarthritis: A systematic review. Revista Brasileira de Geriatria e Gerontologia 19(1):153–164.Viguet-Carrin, S., P. Garnero, and P. D. Delmas. 2006. The role of collagen in bone strength. Osteoporosis International 17(3):319–336.

[42] Shuster S. (2005). Osteoporosis, a unitary hypothesis of collagen loss in skin and bone. Medical hypotheses, 65(3), 426–432. https://doi.org/10.1016/j.mehy.2005.04.027

[43] Kumar, S., Sugihara, F., Suzuki, K., Inoue, N., & Venkateswarathirukumara, S. (2014). A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of

collagen peptide on osteoarthritis. Journal of the Science of Food and Agriculture, 95(4), 702–707. https://doi.org/10.1002/jsfa.6752

[44] Elam, M. L., Johnson, S. A., Hooshmand, S., Feresin, R. G., Payton, M. E., Gu, J., & Arjmandi, B. H. (2015). A calcium-collagen chelate dietary supplement attenuates bone loss in postmenopausal women with osteopenia: a randomized controlled trial. Journal of medicinal food, 18(3), 324–331. https://doi.org/10.1089/jmf.2014.0100

[45] Praet, S., Purdam, C. R., Welvaert, M., Vlahovich, N., Lovell, G., Burke, L. M., Gaida, J. E., Manzanero, S., Hughes, D., & Waddington, G. (2019). Oral Supplementation of Specific Collagen Peptides Combined with Calf-Strengthening Exercises Enhances Function and Reduces Pain in Achilles Tendinopathy Patients. Nutrients, 11(1), 76. https://doi.org/10.3390/nu11010076

[46] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[47] Wang, W., Wu, Z., Dai, Z., Yang, Y., Wang, J., & Wu, G. (2013). Glycine metabolism in animals and humans: implications for nutrition and health. Amino acids, 45(3), 463–477. https://doi.org/10.1007/s00726-013-1493-1

[48] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[49] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[50] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[51] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[52] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[53] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[54] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[55] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[56] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for

collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[57] Slatter, D. A., & Farndale, R. W. (2015). Structural constraints on the evolution of the collagen fibril: convergence on a 1014-residue COL domain. Open biology, 5(5), 140220. https://doi.org/10.1098/rsob.140220

[58] Cianciosi, S. C., & Hird, F. J. (1986). The collagen content of selected animals. Comparative biochemistry and physiology. B, Comparative biochemistry, 85(2), 295–298. https://doi.org/10.1016/0305-0491(86)90003-9

[59] Houck, J.C., de Hesse, C., & Jacob, R.A. (1967). The effect of ageing upon collagen metabolism. Symposia of the Society for Experimental Biology, 21, 403-25 .

[60] Houck, J.C., de Hesse, C., & Jacob, R.A. (1967). The effect of ageing upon collagen metabolism. Symposia of the Society for Experimental Biology, 21, 403-25 .

[61] Lodish H, Berk A, Zipursky SL, et al. Collagen: The Fibrous Proteins of the Matrix. Molecular Cell Biology, 4th Edition. 2000.

[62] Park, J., & Schwartz. (2012). Ingestion of BioCell Collagen®, a novel hydrolyzed chicken sternal cartilage extract; enhanced blood microcirculation and reduced facial aging signs. Clinical Interventions in Aging, 267. https://doi.org/10.2147/cia.s32836

[63] De Luca, C., Mikhal'chik, E. V., Suprun, M. V., Papacharalambous, M., Truhanov, A. I., & Korkina, L. G. (2016). Skin Antiageing and Systemic Redox Effects of Supplementation with Marine Collagen Peptides and Plant-Derived Antioxidants: A Single-Blind Case-Control Clinical Study. Oxidative medicine and cellular longevity, 2016, 4389410. https://doi.org/10.1155/2016/4389410

[64] Alcock, R. D., Shaw, G. C., & Burke, L. M. (2019). Bone Broth Unlikely to Provide Reliable Concentrations of Collagen Precursors Compared With Supplemental Sources of Collagen Used in Collagen

Research, International Journal of Sport Nutrition and Exercise Metabolism, 29(3), 265-272. Retrieved Nov 1, 2022, from https://journals.humankinetics.com/view/journals/ijsnem/29/3/article-p265.xml

[65] Ricard-Blum S. (2011). The collagen family. Cold Spring Harbor perspectives in biology, 3(1), a004978. https://doi.org/10.1101/cshperspect.a004978

[66] Wikipedia 2022 'Collage', Accessed Online November 2nd 2022: https://en.wikipedia.org/wiki/Collagen

[67] Brodsky & Persikov (2005) 'Molecular Structure of the Collagen Triple Helix', Advances in Protein Chemistry, Volume 70, 2005, Pages 301-339.

[68] Szpak, P. (2011). Fish bone chemistry and ultrastructure: implications for taphonomy and stable isotope analysis. Journal of Archaeological Science, 38(12), 3358–3372. https://doi.org/10.1016/j.jas.2011.07.022

[69] Boot-Handford, R. P., & Tuckwell, D. S. (2003). Fibrillar collagen: the key to vertebrate evolution? A tale of molecular incest. BioEssays : news and reviews in molecular, cellular and developmental biology, 25(2), 142–151. https://doi.org/10.1002/bies.10230

[70] Ricard-Blum S. (2011). The collagen family. Cold Spring Harbor perspectives in biology, 3(1), a004978. https://doi.org/10.1101/cshperspect.a004978

[71] Franzke, C. W., Bruckner, P., & Bruckner-Tuderman, L. (2005). Collagenous transmembrane proteins: recent insights into biology and pathology. The Journal of biological chemistry, 280(6), 4005–4008. https://doi.org/10.1074/jbc.R400034200

[72] Boot-Handford, R. P., & Tuckwell, D. S. (2003). Fibrillar collagen: the key to vertebrate evolution? A tale of molecular incest. BioEssays : news and reviews in molecular, cellular and developmental biology, 25(2), 142–151. https://doi.org/10.1002/bies.10230

[73] Ashokkumar, M., & Ajayan, P. M. (2020). Materials science perspective of multifunctional materials derived from collagen. International Materials Reviews, 66(3), 160–187. https://doi.org/10.1080/09506608.2020.1750807

[74] Lodish, H.F., Berk, A.J., Zipursky, S.L., Matsudaira, P., Baltimore, D., & Darnell, J. (2000). Collagen: The Fibrous Proteins of the Matrix.

[75] Henrisken, K. and M.A. Karsdal, Biochemistry of Collagen, Laminins and Elastin (Second Edition) Chapter 1 - Type 1 collagen. Structure, Function and Biomarkers, 2019: p. 1-12.

[76] Ricard-Blum S. (2011). The collagen family. Cold Spring Harbor perspectives in biology, 3(1), a004978. https://doi.org/10.1101/cshperspect.a004978

[77] Cunniffe, G.M., O'Brien, F.J. Collagen scaffolds for orthopedic regenerative medicine. JOM 63, 66–73 (2011). https://doi.org/10.1007/s11837-011-0061-y

[78] Kumari, S., Panda, T. K., & Pradhan, T. (2017). Lysyl Oxidase: Its Diversity in Health and Diseases. Indian journal of clinical biochemistry : IJCB, 32(2), 134–141. https://doi.org/10.1007/s12291-016-0576-7

[79] Herchenhan, A., Uhlenbrock, F., Eliasson, P., Weis, M., Eyre, D., Kadler, K. E., Magnusson, S. P., & Kjaer, M. (2015). Lysyl Oxidase Activity Is Required for Ordered Collagen Fibrillogenesis by Tendon Cells. The Journal of biological chemistry, 290(26), 16440–16450. https://doi.org/10.1074/jbc.M115.641670

[80] Kouguchi, T., Ohmori, T., Shimizu, M., Takahata, Y., Maeyama, Y., Suzuki, T., Morimatsu, F., & Tanabe, S. (2013). Effects of a chicken collagen hydrolysate on the circulation system in subjects with mild hypertension or high-normal blood pressure. Bioscience, biotechnology, and biochemistry, 77(4), 691–696. https://doi.org/10.1271/bbb.120718

[81] https://en.wikipedia.org/wiki/Collagen

[82] Oesser, S., Adam, M., Babel, W., & Seifert, J. (1999). Oral administration of (14)C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). The Journal of nutrition, 129(10), 1891–1895. https://doi.org/10.1093/jn/129.10.1891

[83] Peterkofsky B. (1991). Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. The American journal of clinical nutrition, 54(6 Suppl), 1135S–1140S. https://doi.org/10.1093/ajcn/54.6.1135s

[84] Agarwal et al (2015). Scurvy in pediatric age group - A disease often forgotten?. Journal of clinical orthopaedics and trauma, 6(2), 101–107. https://doi.org/10.1016/j.jcot.2014.12.003

[85] Gorres, K. L., & Raines, R. T. (2010). Prolyl 4-hydroxylase. Critical reviews in biochemistry and molecular biology, 45(2), 106–124. https://doi.org/10.3109/10409231003627991

[86] Levene, C.I., Shoshan, S., & Bates, C.J. (1972). The effect of ascorbic acid on the cross-linking of collagen during its synthesis by cultured 3T6 fibroblasts. Biochimica et Biophysica Acta, 257, 384-388.

[87] Myllylä, R., Majamaa, K., Günzler, V., Hanauske-Abel, H. M., & Kivirikko, K. I. (1984). Ascorbate is consumed stoichiometrically in the uncoupled reactions catalyzed by prolyl 4-hydroxylase and lysyl hydroxylase. The Journal of biological chemistry, 259(9), 5403–5405.

[88] Toxqui, L., & Vaquero, M.P. (2015). Chronic Iron Deficiency as an Emerging Risk Factor for Osteoporosis: A Hypothesis. Nutrients, 7, 2324 - 2344.

[89] Chan, W., & Rennert, O.M. (1980). The role of copper in iron metabolism. Annals of clinical and laboratory science, 10 4, 338-44 .

[90] Barber, E. F., & Cousins, R. J. (1987). Induction of ceruloplasmin synthesis by retinoic acid in rats: influence of dietary copper and vitamin A status. The Journal of nutrition, 117(9), 1615–1622.

[91] *http://www.namrata.co/collagen-synthesistypes-and-composition-part-2/*.
[92] Harris, E. D., & Percival, S. S. (1991). A role for ascorbic acid in copper transport. The American journal of clinical nutrition, 54(6 Suppl), 1193S–1197S. https://doi.org/10.1093/ajcn/54.6.1193s
[93] Harris, E. D., & Percival, S. S. (1991). A role for ascorbic acid in copper transport. The American journal of clinical nutrition, 54(6 Suppl), 1193S–1197S. https://doi.org/10.1093/ajcn/54.6.1193s
[94] Harris, E. D., & Percival, S. S. (1991). A role for ascorbic acid in copper transport. The American journal of clinical nutrition, 54(6 Suppl), 1193S–1197S. https://doi.org/10.1093/ajcn/54.6.1193s
[95] Lindblad et al (2013). Regulation of Vitamin C Homeostasis during Deficiency. Nutrients, 5(8), 2860–2879.
[96] Fulzele et al (2013). Sodium-dependent vitamin C transporter SVCT2: expression and function in bone marrow stromal cells and in osteogenesis. Stem cell research, 10(1), 36–47.
[97] Barsony et al (2011). Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. The Journal of biological chemistry, 286(12), 10864–10875. https://doi.org/10.1074/jbc.M110.155002
[98] Xiao et al (2005). Ascorbic acid inhibits osteoclastogenesis of RAW264.7 cells induced by receptor activated nuclear factor kappaB ligand (RANKL) in vitro. Journal of endocrinological investigation, 28(3), 253–260. https://doi.org/10.1007/BF03345382
[99] Dixit et al (2015). Vitamin C deficiency in the brain impairs cognition, increases amyloid accumulation and deposition, and oxidative stress in APP/PSEN1 and normally aging mice. ACS chemical neuroscience, 6(4), 570–581. https://doi.org/10.1021/cn500308h
[100] Möbius et al (1996). Permissive role of alpha-tocopherol in the stimulation of aldosterone by sodium depletion in the guinea pig. European journal of endocrinology, 134(6), 758–763.

[101] Redmann et al (1995). Ascorbate depletion prevents aldosterone stimulation by sodium deficiency in the guinea pig. European journal of endocrinology, 133(4), 499–506.

[102] Kodama et al (2003). Negative balance of calcium and magnesium under relatively low sodium intake in humans. Journal of nutritional science and vitaminology, 49(3), 201–209. https://doi.org/10.3177/jnsv.49.201

[103] Nishimuta et al (2005). Positive correlation between dietary intake of sodium and balances of calcium and magnesium in young Japanese adults--low sodium intake is a risk factor for loss of calcium and magnesium--. Journal of nutritional science and vitaminology, 51(4), 265–270.

[104] Nishimuta et al (2018). Dietary Salt (Sodium Chloride) Requirement and Adverse Effects of Salt Restriction in Humans. Journal of nutritional science and vitaminology, 64(2), 83–89.

[105] Carbone et al (2016). Sodium Intake and Osteoporosis. Findings From the Women's Health Initiative. The Journal of clinical endocrinology and metabolism, 101(4), 1414–1421. https://doi.org/10.1210/jc.2015-4017

[106] Miyazaki et al (2010). Chronic hyponatremia impairs memory in rats: effects of vasopressin antagonist tolvaptan. The Journal of endocrinology, 206(1), 105–111. https://doi.org/10.1677/JOE-10-0050

[107] Halsted C. H. (2003). Absorption of water-soluble vitamins. Current opinion in gastroenterology, 19(2), 113–117. https://doi.org/10.1097/00001574-200303000-00003

[108] Liguori et al (2018). Oxidative stress, aging, and diseases. Clinical interventions in aging, 13, 757–772. https://doi.org/10.2147/CIA.S158513

[109] Health Effects Institute. 2018. State of Global Air 2018. Special Report. Boston, MA:Health Effects Institute.

[110] Health Effects Institute. 2018. State of Global Air 2018. Special Report. Boston, MA:Health Effects Institute.

[111] Voiland (2010) 'UV Exposure Has Increased Over the Last 30 Years, but Stabilized Since the Mid-1990s', NASA, https://www.nasa.gov/topics/solarsystem/features/uv-exposure.html

[112] Rinnerthaler, M., Bischof, J., Streubel, M. K., Trost, A., & Richter, K. (2015). Oxidative stress in aging human skin. Biomolecules, 5(2), 545–589. https://doi.org/10.3390/biom5020545

[113] Monboisse, J. C., & Borel, J. P. (1992). Oxidative damage to collagen. EXS, 62, 323–327. https://doi.org/10.1007/978-3-0348-7460-1_32

[114] Rattan et al (2013). Hormesis-based anti-aging products: a case study of a novel cosmetic. Dose-response : a publication of International Hormesis Society, 11(1), 99–108. https://doi.org/10.2203/dose-response.11-054.Rattan

[115] Kunutsor, S. K., Laukkanen, T., & Laukkanen, J. A. (2018). Longitudinal associations of sauna bathing with inflammation and oxidative stress: the KIHD prospective cohort study. Annals of medicine, 50(5), 437–442. https://doi.org/10.1080/07853890.2018.1489143

[116] Patrick, R.P., & Johnson, T.L. (2021). Sauna use as a lifestyle practice to extend healthspan. Experimental Gerontology, 154.

[117] Koyama, K. (2014). Exercise-induced oxidative stress: A tool for “hormesis” and “adaptive response.” The Journal of Physical Fitness and Sports Medicine, 3(1), 115–120. https://doi.org/10.7600/jpfsm.3.115

[118] Radak et al (2008). Exercise, oxidative stress and hormesis. Ageing research reviews, 7(1), 34–42. https://doi.org/10.1016/j.arr.2007.04.004

[119] Ursini et al (2017). High Prevalence of Achilles Tendon Enthesopathic Changes in Patients with Type 2 Diabetes Without

Peripheral Neuropathy. Journal of the American Podiatric Medical Association, 107(2), 99–105. https://doi.org/10.7547/16-059

[120] Spoendlin, J., Meier, C., Jick, S. S., & Meier, C. R. (2016). Achilles or biceps tendon rupture in women and men with type 2 diabetes: A population-based case-control study. Journal of diabetes and its complications, 30(5), 903–909. https://doi.org/10.1016/j.jdiacomp.2016.02.017

[121] Tella et al (2014). Prevention and treatment of postmenopausal osteoporosis. The Journal of steroid biochemistry and molecular biology, 142, 155–170. https://doi.org/10.1016/j.jsbmb.2013.09.008

[122] Pingel et al (2012). Effects of transdermal estrogen on collagen turnover at rest and in response to exercise in postmenopausal women. Journal of applied physiology (Bethesda, Md. : 1985), 113(7), 1040–1047. https://doi.org/10.1152/japplphysiol.01463.2011

[123] Sekhar et al (2015). Early Menopause in Type 2 Diabetes - A Study from a South Indian Tertiary Care Centre. Journal of clinical and diagnostic research : JCDR, 9(10), OC08–OC10. https://doi.org/10.7860/JCDR/2015/14181.6628

[124] Pantazis, K., Roupas, N. D., Panagopoulos, A., Theodoraki, S., Tsintoni, A., & Kyriazopoulou, V. (2016). Spontaneous rupture of the long head of the biceps tendon in a woman with hypothyroidism: a case report. Journal of medical case reports, 10, 2. https://doi.org/10.1186/s13256-015-0794-2

[125] Tárraga López et al (2011). Osteoporosis in patients with subclinical hypothyroidism treated with thyroid hormone. Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases, 8(3), 44–48.

[126] Moleti et al (2008). Iodine prophylaxis using iodized salt and risk of maternal thyroid failure in conditions of mild iodine deficiency.

The Journal of clinical endocrinology and metabolism, 93(7), 2616–2621.

[127] Bautista AA, Duya JEDL, Sandoval MASSalt-losing nephropathy in hypothyroidismCase Reports 2014;2014:bcr2014203895.

[128] Abate et al (2013) 'Occurrence of tendon pathologies in metabolic disorders', Rheumatology, Volume 52, Issue 4, April 2013, Pages 599–608.

[129] Lin et al (2017). The effects of high glucose on tendon-derived stem cells: implications of the pathogenesis of diabetic tendon disorders. Oncotarget, 8(11), 17518–17528. https://doi.org/10.18632/oncotarget.15418

[130] Shi et al (2019). Impaired function of tendon-derived stem cells in experimental diabetes mellitus rat tendons: implications for cellular mechanism of diabetic tendon disorder. Stem cell research & therapy, 10(1), 27. https://doi.org/10.1186/s13287-018-1108-6

[131] Lee, J. M., & Veres, S. P. (2019). Advanced glycation end-product cross-linking inhibits biomechanical plasticity and characteristic failure morphology of native tendon. Journal of applied physiology (Bethesda, Md. : 1985), 126(4), 832–841. https://doi.org/10.1152/japplphysiol.00430.2018

[132] Pageon et al (2017) 'Glycation and Skin Aging', Textbook of Aging Skin pp 1247–1270.

[133] Ichihashi et al (2011) 'Glycation Stress and Photo-Aging in Skin', J-Stage, Volume 8 Issue 3 Pages 23-29.

[134] Kessler et al (2014). Enhancement of Achilles tendon repair mediated by matrix metalloproteinase inhibition via systemic administration of doxycycline. Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 32(4), 500–506. https://doi.org/10.1002/jor.22564

[135] Pageon et al (2007). Collagen glycation triggers the formation of aged skin in vitro. European journal of dermatology : EJD, 17(1),

12–20. https://doi.org/10.1684/ejd.2007.0102

[136] Chen et al (2017). Advanced glycation end products decrease collagen I levels in fibroblasts from the vaginal wall of patients with POP via the RAGE, MAPK and NF-κB pathways. International journal of molecular medicine, 40(4), 987–998. https://doi.org/10.3892/ijmm.2017.3097

[137] Fisher et al (2002). Mechanisms of photoaging and chronological skin aging. Archives of dermatology, 138(11), 1462–1470. https://doi.org/10.1001/archderm.138.11.1462

[138] Yamauchi et al (1991). Collagen cross-linking in sun-exposed and unexposed sites of aged human skin. The Journal of investigative dermatology, 97(5), 938–941. https://doi.org/10.1111/1523-1747.ep12491727

[139] Corstjens et al (2008). Glycation associated skin autofluorescence and skin elasticity are related to chronological age and body mass index of healthy subjects. Experimental gerontology, 43(7), 663–667. https://doi.org/10.1016/j.exger.2008.01.012

[140] Adeva-Andany et al (2018). Insulin resistance and glycine metabolism in humans. Amino acids, 50(1), 11–27. https://doi.org/10.1007/s00726-017-2508-0

[141] Wang et al (2019). Glycine Suppresses AGE/RAGE Signaling Pathway and Subsequent Oxidative Stress by Restoring Glo1 Function in the Aorta of Diabetic Rats and in HUVECs. Oxidative medicine and cellular longevity, 2019, 4628962. https://doi.org/10.1155/2019/4628962

[142] Sekhar (2022) 'GlyNAC (Glycine and N-Acetylcysteine) Supplementation Improves Impaired Mitochondrial Fuel Oxidation and Lowers Insulin Resistance in Patients with Type 2 Diabetes: Results of a Pilot Study', Antioxidants 11(1):154.

[143] Vieira et al (2015). Glycine improves biochemical and biomechanical properties following inflammation of the achilles tendon. Anatomical record (Hoboken, N.J. : 2007), 298(3), 538–545. https://doi.org/10.1002/ar.23041

[144] Dakshinamurti K. (2015). Vitamins and their derivatives in the prevention and treatment of metabolic syndrome diseases (diabetes). Canadian journal of physiology and pharmacology, 93(5), 355–362.

[145] Freund et al (2018). The Inhibition of Advanced Glycation End Products by Carnosine and Other Natural Dipeptides to Reduce Diabetic and Age-Related Complications. Comprehensive reviews in food science and food safety, 17(5), 1367–1378.

[146] Cefalu et al (1995). Caloric restriction decreases age-dependent accumulation of the glycoxidation products, N epsilon-(carboxymethyl)lysine and pentosidine, in rat skin collagen. The journals of gerontology. Series A, Biological sciences and medical sciences, 50(6), B337–B341. https://doi.org/10.1093/gerona/50a.6.b337

[147] Kim, C. S., Park, S., & Kim, J. (2017). The role of glycation in the pathogenesis of aging and its prevention through herbal products and physical exercise. Journal of exercise nutrition & biochemistry, 21(3), 55–61. https://doi.org/10.20463/jenb.2017.0027

[148] Dideriksen et al (2017). Tendon collagen synthesis declines with immobilization in elderly humans: no effect of anti-inflammatory medication. Journal of applied physiology (Bethesda, Md. : 1985), 122(2), 273–282. https://doi.org/10.1152/japplphysiol.00809.2015

[149] Danby F. W. (2010). Nutrition and aging skin: sugar and glycation. Clinics in dermatology, 28(4), 409–411. https://doi.org/10.1016/j.clindermatol.2010.03.018

[150] Berge et al (2007). Sugar-induced premature aging and altered differentiation in human epidermal keratinocytes. Annals of the New York Academy of Sciences, 1100, 524–529. https://doi.org/10.1196/annals.1395.058

[151] Urbach and Lentz (1945) ‘Carbohydrate metabolism and the skin’. Arch Dermatol Syphilol 1945;52:301-16.

[152] Aragno, M., & Mastrocola, R. (2017). Dietary Sugars and Endogenous Formation of Advanced Glycation Endproducts: Emerging Mechanisms of Disease. Nutrients, 9(4), 385. https://doi.org/10.3390/nu9040385

[153] Gugliucci A. (2017). Formation of Fructose-Mediated Advanced Glycation End Products and Their Roles in Metabolic and Inflammatory Diseases. Advances in nutrition (Bethesda, Md.), 8(1), 54–62. https://doi.org/10.3945/an.116.013912

[154] Levi and Werman (1998) 'Long-Term Fructose Consumption Accelerates Glycation and Several Age-Related Variables in Male Rats', The Journal of Nutrition, Volume 128, Issue 9, September 1998, Pages 1442–1449.

[155] Mark et al (2014) 'Consumption of a Diet Low in Advanced Glycation End Products for 4 Weeks Improves Insulin Sensitivity in Overweight Women', Diabetes Care 1 January 2014; 37 (1): 88–95.

[156] LeWine (2008) 'Glycemic index for 60+ foods', Harvard EDU, Accessed Online Nov 26th 2022: https://www.health.harvard.edu/diseases-and-conditions/glycemic-index-and-glycemic-load-for-100-foods

[157] Tsuzaki et al (2003). IL-1 beta induces COX2, MMP-1, -3 and -13, ADAMTS-4, IL-1 beta and IL-6 in human tendon cells. Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 21(2), 256–264. https://doi.org/10.1016/S0736-0266(02)00141-9

[158] DiNicolantonio, J. J., O'Keefe, J. H., & McCarty, M. F. (2017). Supplemental N-acetylcysteine and other measures that boost intracellular glutathione can downregulate interleukin-1β signalling: a potential strategy for preventing cardiovascular events?. Open heart, 4(2), e000599. https://doi.org/10.1136/openhrt-2017-000599

[159] DiNicolantonio, J. J., O'Keefe, J. H., & McCarty, M. F. (2017). Supplemental N-acetylcysteine and other measures that boost intracellular glutathione can downregulate interleukin-1β signalling: a

potential strategy for preventing cardiovascular events?. Open heart, 4(2), e000599. https://doi.org/10.1136/openhrt-2017-000599

[160] Galus, R., Antiszko, M., & Włodarski, P. (2006). Zastosowanie kwasu hialuronowego w medycynie klinicznej [Clinical applications of hyaluronic acid]. Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego, 20(119), 606–608.

[161] Aslam et al (2006). Pomegranate as a cosmeceutical source: pomegranate fractions promote proliferation and procollagen synthesis and inhibit matrix metalloproteinase-1 production in human skin cells. Journal of ethnopharmacology, 103(3), 311–318. https://doi.org/10.1016/j.jep.2005.07.027

[162] Martineau et al (2006). Anti-diabetic properties of the Canadian lowbush blueberry Vaccinium angustifolium Ait. Phytomedicine : international journal of phytotherapy and phytopharmacology, 13(9-10), 612–623. https://doi.org/10.1016/j.phymed.2006.08.005

[163] Fernandez-Gomez et al (2018). Inhibitors of advanced glycation end products from coffee bean roasting by-product. European Food Research and Technology, 244(6), 1101–1110. https://doi.org/10.1007/s00217-017-3023-y

[164] Mizutani et al (2000). Resveratrol inhibits AGEs-induced proliferation and collagen synthesis activity in vascular smooth muscle cells from stroke-prone spontaneously hypertensive rats. Biochemical and biophysical research communications, 274(1), 61–67. https://doi.org/10.1006/bbrc.2000.3097

[165] Dearlove et al (2008). Inhibition of protein glycation by extracts of culinary herbs and spices. Journal of medicinal food, 11(2), 275–281. https://doi.org/10.1089/jmf.2007.536

[166] Nguyen, H. P., & Katta, R. (2015). Sugar Sag: Glycation and the Role of Diet in Aging Skin. Skin therapy letter, 20(6), 1–5.

[167] Fukami et al (2013). Potential inhibitory effects of L-carnitine supplementation on tissue advanced glycation end products in

patients with hemodialysis. Rejuvenation research, 16(6), 460–466. https://doi.org/10.1089/rej.2013.1459

[168] Muto et al (2014). Temporary inductions of matrix metalloprotease-3 (MMP-3) expression and cell apoptosis are associated with tendon degeneration or rupture after corticosteroid injection. Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 32(10), 1297–1304. https://doi.org/10.1002/jor.22681

[169] Vallone, G., & Vittorio, T. (2014). Complete Achilles tendon rupture after local infiltration of corticosteroids in the treatment of deep retrocalcaneal bursitis. Journal of ultrasound, 17(2), 165–167. https://doi.org/10.1007/s40477-014-0066-9

[170] Taguchi et al (2016). Quantitative and Qualitative Change of Collagen of Achilles Tendons in Rats With Systemic Administration of Glucocorticoids. Foot & ankle international, 37(3), 327–333. https://doi.org/10.1177/1071100715613138

[171] Chen et al (2015). Dexamethasone inhibits the differentiation of rat tendon stem cells into tenocytes by targeting the scleraxis gene. The Journal of steroid biochemistry and molecular biology, 152, 16–24. https://doi.org/10.1016/j.jsbmb.2015.04.010

[172] Menon et al (2013). New insights in extracellular matrix remodeling and collagen turnover related pathways in cultured human tenocytes after ciprofloxacin administration. Muscles, ligaments and tendons journal, 3(3), 122–131.

[173] Fox et al (2014). Fluoroquinolones impair tendon healing in a rat rotator cuff repair model: a preliminary study. The American journal of sports medicine, 42(12), 2851–2859. https://doi.org/10.1177/0363546514545858

[174] Daneman, N., Lu, H., & Redelmeier, D. A. (2015). Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ open, 5(11), e010077. https://doi.org/10.1136/bmjopen-2015-010077

[175] de Oliveira et al (2015). Structural and biomechanical changes in the Achilles tendon after chronic treatment with statins. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, 77, 50–57. https://doi.org/10.1016/j.fct.2014.12.014

[176] Grover, M., He, C., Hsieh, M.-C., & Yu, S.-S. (2015). A Chemical Engineering Perspective on the Origins of Life. Processes, 3(2), 309–338. https://doi.org/10.3390/pr3020309

[177] The Nobel Prize in Chemistry 1989. NobelPrize.org. Nobel Prize Outreach AB 2022. Fri. 4 Nov 2022. <https://www.nobelprize.org/prizes/chemistry/1989/summary/>

[178] Andras, P., & Andras, C. (2005). The origins of life -- the 'protein interaction world' hypothesis: protein interactions were the first form of self-reproducing life and nucleic acids evolved later as memory molecules. Medical hypotheses, 64(4), 678–688. https://doi.org/10.1016/j.mehy.2004.11.029

[179] Ikehara K. (2014). [GADV]-protein world hypothesis on the origin of life. Origins of life and evolution of the biosphere : the journal of the International Society for the Study of the Origin of Life, 44(4), 299–302. https://doi.org/10.1007/s11084-014-9383-4

[180] Ikehara K. (2005). Possible steps to the emergence of life: the [GADV]-protein world hypothesis. Chemical record (New York, N.Y.), 5(2), 107–118. https://doi.org/10.1002/tcr.20037

[181] Schomburg, I., Chang, A., Placzek, S., Söhngen, C., Rother, M., Lang, M., Munaretto, C., Ulas, S., Stelzer, M., Grote, A., Scheer, M., & Schomburg, D. (2013). BRENDA in 2013: integrated reactions, kinetic data, enzyme function data, improved disease classification: new options and contents in BRENDA. Nucleic acids research, 41(Database issue), D764–D772. https://doi.org/10.1093/nar/gks1049

[182] Iqubal, M. A., Sharma, R., Jheeta, S., & Kamaluddin (2017). Thermal Condensation of Glycine and Alanine on Metal Ferrite

Surface: Primitive Peptide Bond Formation Scenario. Life (Basel, Switzerland), 7(2), 15. https://doi.org/10.3390/life7020015

[183] Grover, M., He, C., Hsieh, M.-C., & Yu, S.-S. (2015). A Chemical Engineering Perspective on the Origins of Life. Processes, 3(2), 309–338. https://doi.org/10.3390/pr3020309

[184] Iqubal, M. A., Sharma, R., Jheeta, S., & Kamaluddin (2017). Thermal Condensation of Glycine and Alanine on Metal Ferrite Surface: Primitive Peptide Bond Formation Scenario. Life (Basel, Switzerland), 7(2), 15. https://doi.org/10.3390/life7020015

[185] Iqubal, M. A., Sharma, R., Jheeta, S., & Kamaluddin (2017). Thermal Condensation of Glycine and Alanine on Metal Ferrite Surface: Primitive Peptide Bond Formation Scenario. Life (Basel, Switzerland), 7(2), 15. https://doi.org/10.3390/life7020015

[186] Fitz D et al. Chemical evolution toward the origin of life. Pure Appl Chem. 2007,79(12),2101-2117.

[187] Fitz D et al. Chemical evolution toward the origin of life. Pure Appl Chem. 2007,79(12),2101-2117.

[188] Fitz D et al. Chemical evolution toward the origin of life. Pure Appl Chem. 2007,79(12),2101-2117.

[189] Wilde, S. A., Valley, J. W., Peck, W. H., & Graham, C. M. (2001). Evidence from detrital zircons for the existence of continental crust and oceans on the Earth 4.4 Gyr ago. Nature, 409(6817), 175–178. https://doi.org/10.1038/35051550

[190] Mojzsis, S. J., Harrison, T. M., & Pidgeon, R. T. (2001). Oxygen-isotope evidence from ancient zircons for liquid water at the Earth's surface 4,300 Myr ago. Nature, 409(6817), 178–181. https://doi.org/10.1038/35051557

[191] Fitz D et al. Chemical evolution toward the origin of life. Pure Appl Chem. 2007,79(12),2101-2117.

[192] Hagemann M. (2011). Molecular biology of cyanobacterial salt acclimation. FEMS microbiology reviews, 35(1), 87–123.

https://doi.org/10.1111/j.1574-6976.2010.00234.x
[193] Fitz D et al. Chemical evolution toward the origin of life. Pure Appl Chem. 2007,79(12),2101-2117.
[194] Hagemann M. (2011). Molecular biology of cyanobacterial salt acclimation. FEMS microbiology reviews, 35(1), 87–123. https://doi.org/10.1111/j.1574-6976.2010.00234.x
[195] Fariduddin, Q., Varshney, P., Yusuf, M., Ali, A., & Ahmad, A. (2013). Dissecting the Role of Glycine Betaine in Plants under Abiotic Stress.
[196] Fariduddin, Q., Varshney, P., Yusuf, M., Ali, A., & Ahmad, A. (2013). Dissecting the Role of Glycine Betaine in Plants under Abiotic Stress.
[197] Hagemann M. (2011). Molecular biology of cyanobacterial salt acclimation. FEMS microbiology reviews, 35(1), 87–123. https://doi.org/10.1111/j.1574-6976.2010.00234.x
[198] Hussy, N., Deleuze, C., Pantaloni, A., Desarménien, M. G., & Moos, F. (1997). Agonist action of taurine on glycine receptors in rat supraoptic magnocellular neurones: possible role in osmoregulation. The Journal of physiology, 502 (Pt 3)(Pt 3), 609–621. https://doi.org/10.1111/j.1469-7793.1997.609bj.x
[199] Dvoráková-Holá, K., Matusková, A., Kubala, M., Otyepka, M., Kucera, T., Vecer, J., Herman, P., Parkhomenko, N., Kutejova, E., & Janata, J. (2010). Glycine-rich loop of mitochondrial processing peptidase alpha-subunit is responsible for substrate recognition by a mechanism analogous to mitochondrial receptor Tom20. Journal of molecular biology, 396(5), 1197–1210. https://doi.org/10.1016/j.jmb.2009.12.054
[200] Hagemann M. (2011). Molecular biology of cyanobacterial salt acclimation. FEMS microbiology reviews, 35(1), 87–123. https://doi.org/10.1111/j.1574-6976.2010.00234.x
[201] Beyoğlu, D., & Idle, J. R. (2012). The glycine deportation system and its pharmacological consequences. Pharmacology &

therapeutics, 135(2), 151–167. https://doi.org/10.1016/j.pharmthera.2012.05.003

[202] Steigerwald (2009) 'NASA Researchers Make First Discovery of Life's Building Block in Comet', NASA: https://www.nasa.gov/mission_pages/stardust/news/stardust_amino_acid.html

[203] Kvenvolden, K., Lawless, J., Pering, K., Peterson, E., Flores, J., Ponnamperuma, C., Kaplan, I. R., & Moore, C. (1970). Evidence for extraterrestrial amino-acids and hydrocarbons in the Murchison meteorite. Nature, 228(5275), 923–926. https://doi.org/10.1038/228923a0

[204] Snyder, L.E., Lovas, F.J., Hollis, J.M., Friedel, D.N., Jewell, P.R., Remijan, A.J., Ilyushin, V.V., Alekseev, E.A., & Dyubko, S.F. (2004). A Rigorous Attempt to Verify Interstellar Glycine. The Astrophysical Journal, 619, 914 - 930.

[205] Max-Planck-Gesellschaft. (2008, March 27). Organic Molecule, Amino Acid-Like, Found In Constellation Sagittarius. ScienceDaily. Retrieved November 2, 2022 from www.sciencedaily.com/releases/2008/03/080326161658.htm

[206] Beyoğlu, D., & Idle, J. R. (2012). The glycine deportation system and its pharmacological consequences. Pharmacology & therapeutics, 135(2), 151–167. https://doi.org/10.1016/j.pharmthera.2012.05.003

[207] Briggs, R., Ertem, G., Ferris, J. P., Greenberg, J. M., McCain, P. J., Mendoza-Gomez, C. X., & Schutte, W. (1992). Comet Halley as an aggregate of interstellar dust and further evidence for the photochemical formation of organics in the interstellar medium. Origins of life and evolution of the biosphere : the journal of the International Society for the Study of the Origin of Life, 22(5), 287–307. https://doi.org/10.1007/BF01810858

[208] Goldman, N., Reed, E. J., Fried, L. E., William Kuo, I. F., & Maiti, A. (2010). Synthesis of glycine-containing complexes in

impacts of comets on early Earth. Nature chemistry, 2(11), 949–954. https://doi.org/10.1038/nchem.827

[209] MILLER S. L. (1953). A production of amino acids under possible primitive earth conditions. Science (New York, N.Y.), 117(3046), 528–529. https://doi.org/10.1126/science.117.3046.528

[210] Kotler, J. M., Hinman, N. W., Yan, B., Stoner, D. L., & Scott, J. R. (2008). Glycine identification in natural jarosites using laser desorption Fourier transform mass spectrometry: implications for the search for life on Mars. Astrobiology, 8(2), 253–266. https://doi.org/10.1089/ast.2006.0102

[211] Beyoğlu, D., & Idle, J. R. (2012). The glycine deportation system and its pharmacological consequences. Pharmacology & therapeutics, 135(2), 151–167. https://doi.org/10.1016/j.pharmthera.2012.05.003

[212] Kikuchi G. (1973). The glycine cleavage system: composition, reaction mechanism, and physiological significance. Molecular and cellular biochemistry, 1(2), 169–187. https://doi.org/10.1007/BF01659328

[213] Bernhardt, H. S., & Patrick, W. M. (2014). Genetic code evolution started with the incorporation of glycine, followed by other small hydrophilic amino acids. Journal of molecular evolution, 78(6), 307–309. https://doi.org/10.1007/s00239-014-9627-y

[214] Ntountoumi, C., Vlastaridis, P., Mossialos, D., Stathopoulos, C., Iliopoulos, I., Promponas, V., Oliver, S. G., & Amoutzias, G. D. (2019). Low complexity regions in the proteins of prokaryotes perform important functional roles and are highly conserved. Nucleic acids research, 47(19), 9998–10009. https://doi.org/10.1093/nar/gkz730

[215] Chaliotis, A., Vlastaridis, P., Mossialos, D., Ibba, M., Becker, H. D., Stathopoulos, C., & Amoutzias, G. D. (2017). The complex evolutionary history of aminoacyl-tRNA synthetases. Nucleic acids research, 45(3), 1059–1068. https://doi.org/10.1093/nar/gkw1182

[216] Higgs, P. G., & Pudritz, R. E. (2009). A thermodynamic basis for prebiotic amino acid synthesis and the nature of the first genetic code. Astrobiology, 9(5), 483–490. https://doi.org/10.1089/ast.2008.0280

[217] Trifonov E. N. (2000). Consensus temporal order of amino acids and evolution of the triplet code. Gene, 261(1), 139–151. https://doi.org/10.1016/s0378-1119(00)00476-5

[218] Plimmer, R.H.A. (1912) [1908]. Plimmer, R.H.A.; Hopkins, F.G. (eds.). The chemical composition of the proteins. Monographs on biochemistry. Vol. Part I. Analysis (2nd ed.). London: Longmans, Green and Co. p. 82.

[219] Braconnot, Henri (1820). "Sur la conversion des matières animales en nouvelles substances par le moyen de l'acide sulfurique" [On the conversion of animal materials into new substances by means of sulfuric acid]. Annales de Chimie et de Physique. 2nd series (in French). 13: 113–125. ; see p. 114.

[220] Boussingault (1838). "Sur la composition du sucre de gélatine et de l'acide nitro-saccharique de Braconnot" [On the composition of sugar of gelatine and of nitro-glucaric acid of Braconnot]. Comptes Rendus (in French). 7: 493–495.

[221] Berzelius, Jacob (1848). Jahres-Bericht über die Fortschritte der Chemie und Mineralogie (Annual Report on the Progress of Chemistry and Mineralogy). Vol. 47. Tübigen, (Germany): Laupp. p. 654. From p. 654

[222] Nye, Mary Jo (1999). Before Big Science: The Pursuit of Modern Chemistry and Physics, 1800-1940. Harvard University Press. ISBN 9780674063822.

[223] ARNSTEIN H. R. (1954). The metabolism of glycine. Advances in protein chemistry, 9, 1–91. https://doi.org/10.1016/s0065-3233(08)60204-1

[224] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic

capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[225] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[226] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[227] Meléndez-Hevia, E., & de Paz-Lugo, P. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of Biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[228] Boot-Handford, R.P., & Tuckwell, D.S. (2003). Fibrillar collagen: The key to vertebrate evolution? A tale of molecular incest. BioEssays, 25.

[229] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[230] Kielty, C. M., Sherratt, M. J., & Shuttleworth, C. A. (2002). Elastic fibres. Journal of cell science, 115(Pt 14), 2817–2828. https://doi.org/10.1242/jcs.115.14.2817

[231] Kaufman, M. J., Prescot, A. P., Ongur, D., Evins, A. E., Barros, T. L., Medeiros, C. L., Covell, J., Wang, L., Fava, M., & Renshaw, P. F. (2009). Oral glycine administration increases brain glycine/creatine ratios in men: a proton magnetic resonance spectroscopy study. Psychiatry research, 173(2), 143–149. https://doi.org/10.1016/j.pscychresns.2009.03.004

[232] Sekhar, R. V., Patel, S. G., Guthikonda, A. P., Reid, M., Balasubramanyam, A., Taffet, G. E., & Jahoor, F. (2011). Deficient

synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. The American journal of clinical nutrition, 94(3), 847–853. https://doi.org/10.3945/ajcn.110.003483

[233] Jackson A. A. (1991). The glycine story. European journal of clinical nutrition, 45(2), 59–65.

[234] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[235] Persaud, C., Forrester, T., & Jackson, A. A. (1996). Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. The Journal of nutrition, 126(11), 2823–2830. https://doi.org/10.1093/jn/126.11.2823

[236] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[237] ARNSTEIN, H. R., & STANKOVIC, V. (1956). The effect of certain vitamin deficiencies on glycine biosynthesis. The Biochemical journal, 62(2), 190–198. https://doi.org/10.1042/bj0620190

[238] Melendez-Hevia, E., & Paz-Lugo, P. D. (2008). Branch-point stoichiometry can generate weak links in metabolism: the case of glycine biosynthesis. Journal of biosciences, 33(5), 771–780. https://doi.org/10.1007/s12038-008-0097-5

[239] Jackson A. A. (1991). The glycine story. European journal of clinical nutrition, 45(2), 59–65.

[240] Weissengruber, G. E., Fuss, F. K., Egger, G., Stanek, G., Hittmair, K. M., & Forstenpointner, G. (2006). The elephant knee joint: morphological and biomechanical considerations. Journal of

anatomy, 208(1), 59–72. https://doi.org/10.1111/j.1469-7580.2006.00508.x

[241] Wallach J. D. (1967). Degenerative arthritis in a black rhinoceros. Journal of the American Veterinary Medical Association, 151(7), 887–889.

[242] Kuyinu, E. L., Narayanan, G., Nair, L. S., & Laurencin, C. T. (2016). Animal models of osteoarthritis: classification, update, and measurement of outcomes. Journal of orthopaedic surgery and research, 11, 19. https://doi.org/10.1186/s13018-016-0346-5

[243] Cohen-Solal, M., Funck-Brentano, T., & Hay, E. (2013). Animal models of osteoarthritis for the understanding of the bone contribution. BoneKEy reports, 2, 422. https://doi.org/10.1038/bonekey.2013.156

[244] Anné, J., Hedrick, B. P., & Schein, J. P. (2016). First diagnosis of septic arthritis in a dinosaur. Royal Society Open Science, 3(8), 160222. https://doi.org/10.1098/rsos.160222

[245] Rothschild (1990) 'Radiologic assessment of osteoarthritis in dinosaurs', Annals of Carnegie Museum 59(4):295-301.

[246] Wu, G., Fang, Y. Z., Yang, S., Lupton, J. R., & Turner, N. D. (2004). Glutathione metabolism and its implications for health. The Journal of nutrition, 134(3), 489–492. https://doi.org/10.1093/jn/134.3.489

[247] Pompella, A., Visvikis, A., Paolicchi, A., De Tata, V., & Casini, A. F. (2003). The changing faces of glutathione, a cellular protagonist. Biochemical pharmacology, 66(8), 1499–1503. https://doi.org/10.1016/s0006-2952(03)00504-5

[248] Wu, G., Fang, Y. Z., Yang, S., Lupton, J. R., & Turner, N. D. (2004). Glutathione metabolism and its implications for health. The Journal of nutrition, 134(3), 489–492. https://doi.org/10.1093/jn/134.3.489

[249] Sekhar, R. V., Patel, S. G., Guthikonda, A. P., Reid, M., Balasubramanyam, A., Taffet, G. E., & Jahoor, F. (2011). Deficient

synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. The American journal of clinical nutrition, 94(3), 847–853. https://doi.org/10.3945/ajcn.110.003483

[250] White, C. C., Viernes, H., Krejsa, C. M., Botta, D., & Kavanagh, T. J. (2003). Fluorescence-based microtiter plate assay for glutamate-cysteine ligase activity. Analytical biochemistry, 318(2), 175–180. https://doi.org/10.1016/s0003-2697(03)00143-x

[251] Pizzorno J. (2014). Glutathione!. Integrative medicine (Encinitas, Calif.), 13(1), 8–12.

[252] McCarty, M. F., O'Keefe, J. H., & DiNicolantonio, J. J. (2018). Dietary Glycine Is Rate-Limiting for Glutathione Synthesis and May Have Broad Potential for Health Protection. The Ochsner journal, 18(1), 81–87.

[253] Franco, R., Schoneveld, O. J., Pappa, A., & Panayiotidis, M. I. (2007). The central role of glutathione in the pathophysiology of human diseases. Archives of physiology and biochemistry, 113(4-5), 234–258. https://doi.org/10.1080/13813450701661198

[254] Lu S. C. (2013). Glutathione synthesis. Biochimica et biophysica acta, 1830(5), 3143–3153. https://doi.org/10.1016/j.bbagen.2012.09.008

[255] Dodd, S., Dean, O., Copolov, D. L., Malhi, G. S., & Berk, M. (2008). N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. Expert opinion on biological therapy, 8(12), 1955–1962. https://doi.org/10.1517/14728220802517901

[256] Atkuri et al (2007) 'N-Acetylcysteine—a safe antidote for cysteine/glutathione deficiency', Current Opinion in Pharmacology, Volume 7, Issue 4, August 2007, Pages 355-359.

[257] Sekhar, R. V., Patel, S. G., Guthikonda, A. P., Reid, M., Balasubramanyam, A., Taffet, G. E., & Jahoor, F. (2011). Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. The

American journal of clinical nutrition, 94(3), 847–853. https://doi.org/10.3945/ajcn.110.003483

[258] McCarty, M. F., DiNicolantonio, J. J., & Lerner, A. (2021). Review - Nutraceuticals Can Target Asthmatic Bronchoconstriction: NADPH Oxidase-Dependent Oxidative Stress, RhoA and Calcium Dynamics. Journal of asthma and allergy, 14, 685–701. https://doi.org/10.2147/JAA.S307549

[259] DiNicolantonio et al (2019) 'Activated Glycine Receptors May Decrease Endosomal NADPH Oxidase Activity by Opposing ClC-3-Mediated Efflux of Chloride from Endosomes', Medical Hypotheses 123(1).

[260] Brown, D. I., & Griendling, K. K. (2009). Nox proteins in signal transduction. Free radical biology & medicine, 47(9), 1239–1253. https://doi.org/10.1016/j.freeradbiomed.2009.07.023

[261] Meijles, D. N., & Pagano, P. J. (2016). Nox and Inflammation in the Vascular Adventitia. Hypertension, 67(1), 14–19. https://doi.org/10.1161/hypertensionaha.115.03622

[262] Díaz-Flores, M., Cruz, M., Duran-Reyes, G., Munguia-Miranda, C., Loza-Rodríguez, H., Pulido-Casas, E., Torres-Ramírez, N., Gaja-Rodriguez, O., Kumate, J., Baiza-Gutman, L. A., & Hernández-Saavedra, D. (2013). Oral supplementation with glycine reduces oxidative stress in patients with metabolic syndrome, improving their systolic blood pressure. Canadian journal of physiology and pharmacology, 91(10), 855–860. https://doi.org/10.1139/cjpp-2012-0341

[263] Sahin, E., Göçmen, A. Y., Koçak, H., Tuncer, M., & Gümüslü, S. (2008). The association of advanced glycation end-products with glutathione status. Annals of clinical biochemistry, 45(Pt 4), 369–374. https://doi.org/10.1258/acb.2007.007186

[264] Sharma, A. K., Sharma, V. R., Gupta, G. K., Ashraf, G. M., & Kamal, M. A. (2019). Advanced Glycation End Products (AGEs), Glutathione and Breast Cancer: Factors, Mechanism and

Therapeutic Interventions. Current drug metabolism, 20(1), 65–71. https://doi.org/10.2174/1389200219666180912104342

[265] Noe et al (2013) 'Effect of Glycine on Protein Oxidation and Advanced Glycation End Products Formation', Journal of Experimental & Clinical Medicine, Volume 5, Issue 3, June 2013, Pages 109-114.

[266] Wang, Z., Zhang, J., Chen, L., Li, J., Zhang, H., & Guo, X. (2019). Glycine Suppresses AGE/RAGE Signaling Pathway and Subsequent Oxidative Stress by Restoring Glo1 Function in the Aorta of Diabetic Rats and in HUVECs. Oxidative medicine and cellular longevity, 2019, 4628962. https://doi.org/10.1155/2019/4628962

[267] Cruz, M., Maldonado-Bernal, C., Mondragón-Gonzalez, R., Sanchez-Barrera, R., Wacher, N. H., Carvajal-Sandoval, G., & Kumate, J. (2008). Glycine treatment decreases proinflammatory cytokines and increases interferon-gamma in patients with type 2 diabetes. Journal of endocrinological investigation, 31(8), 694–699. https://doi.org/10.1007/BF03346417

[268] Carvajal Sandoval, G., Medina Santillán, R., Juárez, E., RamosMartínez, G., & Carvajal Juárez, M. E. (1999). Effect of glycine on hemoglobin glycation in diabetic patients. Proceedings of the Western Pharmacology Society, 42, 31–32.

[269] McCarty, M. F., DiNicolantonio, J. J., & O'Keefe, J. H. (2022). Nutraceutical Prevention of Diabetic Complications-Focus on Dicarbonyl and Oxidative Stress. Current issues in molecular biology, 44(9), 4314–4338. https://doi.org/10.3390/cimb44090297

[270] Gannon, M. C., Nuttall, J. A., & Nuttall, F. Q. (2002). The metabolic response to ingested glycine. The American journal of clinical nutrition, 76(6), 1302–1307. https://doi.org/10.1093/ajcn/76.6.1302

[271] Attobla, M.B. (2014). Glycine supplementation to improve insulin sensitivity in humans.

[272] McCarty et al (2019) 'Activated Glycine Receptors May Decrease Endosomal NADPH Oxidase Activity by Opposing ClC-3-Mediated Efflux of Chloride from Endosomes', Medical Hypotheses 123, DOI: 10.1016/j.mehy.2019.01.012

[273] Jackson, A. A., Badaloo, A. V., Forrester, T., Hibbert, J. M., & Persaud, C. (1987). Urinary excretion of 5-oxoproline (pyroglutamic aciduria) as an index of glycine insufficiency in normal man. The British journal of nutrition, 58(2), 207–214. https://doi.org/10.1079/bjn19870088

[274] Jackson A. A. (1991). The glycine story. European journal of clinical nutrition, 45(2), 59–65.

[275] Zhong, Z., Wheeler, M. D., Li, X., Froh, M., Schemmer, P., Yin, M., Bunzendaul, H., Bradford, B., & Lemasters, J. J. (2003). L-Glycine: a novel antiinflammatory, immunomodulatory, and cytoprotective agent. Current opinion in clinical nutrition and metabolic care, 6(2), 229–240. https://doi.org/10.1097/00075197-200303000-00013

[276] Cruz, M., Maldonado-Bernal, C., Mondragón-Gonzalez, R., Sanchez-Barrera, R., Wacher, N. H., Carvajal-Sandoval, G., & Kumate, J. (2008). Glycine treatment decreases proinflammatory cytokines and increases interferon-gamma in patients with type 2 diabetes. Journal of endocrinological investigation, 31(8), 694–699. https://doi.org/10.1007/BF03346417

[277] Pompella, A., Visvikis, A., Paolicchi, A., De Tata, V., & Casini, A. F. (2003). The changing faces of glutathione, a cellular protagonist. Biochemical pharmacology, 66(8), 1499–1503. https://doi.org/10.1016/s0006-2952(03)00504-5

[278] Chen, Y., Yang, Y., Miller, M. L., Shen, D., Shertzer, H. G., Stringer, K. F., Wang, B., Schneider, S. N., Nebert, D. W., & Dalton, T. P. (2007). Hepatocyte-specific Gclc deletion leads to rapid onset of steatosis with mitochondrial injury and liver failure. Hepatology (Baltimore, Md.), 45(5), 1118–1128. https://doi.org/10.1002/hep.21635

[279] Sies H. (1999). Glutathione and its role in cellular functions. Free radical biology & medicine, 27(9-10), 916–921. https://doi.org/10.1016/s0891-5849(99)00177-x

[280] Ruiz-Ramírez, A., Ortiz-Balderas, E., Cardozo-Saldaña, G., Diaz-Diaz, E., & El-Hafidi, M. (2014). Glycine restores glutathione and protects against oxidative stress in vascular tissue from sucrose-fed rats. Clinical science (London, England : 1979), 126(1), 19–29. https://doi.org/10.1042/CS20130164

[281] El Hafidi, M., Pérez, I., Zamora, J., Soto, V., Carvajal-Sandoval, G., & Baños, G. (2004). Glycine intake decreases plasma free fatty acids, adipose cell size, and blood pressure in sucrose-fed rats. American journal of physiology. Regulatory, integrative and comparative physiology, 287(6), R1387–R1393. https://doi.org/10.1152/ajpregu.00159.2004

[282] McCarty, M. F., & DiNicolantonio, J. J. (2014). The cardiometabolic benefits of glycine: Is glycine an 'antidote' to dietary fructose?. Open heart, 1(1), e000103. https://doi.org/10.1136/openhrt-2014-000103

[283] McCarty, M. F., & DiNicolantonio, J. J. (2014). The cardiometabolic benefits of glycine: Is glycine an 'antidote' to dietary fructose?. Open heart, 1(1), e000103. https://doi.org/10.1136/openhrt-2014-000103

[284] Bannai, M., & Kawai, N. (2012). New therapeutic strategy for amino acid medicine: glycine improves the quality of sleep. Journal of pharmacological sciences, 118(2), 145–148. https://doi.org/10.1254/jphs.11r04fm

[285] Kawai, N., Sakai, N., Okuro, M., Karakawa, S., Tsuneyoshi, Y., Kawasaki, N., Takeda, T., Bannai, M., & Nishino, S. (2015). The sleep-promoting and hypothermic effects of glycine are mediated by NMDA receptors in the suprachiasmatic nucleus. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 40(6), 1405–1416. https://doi.org/10.1038/npp.2014.326

[286] Bannai, M., Kawai, N., Nagao, K., Nakano, S., Matsuzawa, D., & Shimizu, E. (2011). Oral administration of glycine increases extracellular serotonin but not dopamine in the prefrontal cortex of rats. Psychiatry and clinical neurosciences, 65(2), 142–149. https://doi.org/10.1111/j.1440-1819.2010.02181.x

[287] VIVO Pathophysiology (2018) 'The Pineal Gland and Melatonin', Accessed Online November 6th 2022: http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/otherendo/pineal.html

[288] Yamadera, W., Inagawa, K., Chiba, S. et al. Glycine ingestion improves subjective sleep quality in human volunteers, correlating with polysomnographic changes. Sleep Biol. Rhythms 5, 126–131 (2007). https://doi.org/10.1111/j.1479-8425.2007.00262.x

[289] Buford, T. W., Kreider, R. B., Stout, J. R., Greenwood, M., Campbell, B., Spano, M., Ziegenfuss, T., Lopez, H., Landis, J., & Antonio, J. (2007). International Society of Sports Nutrition position stand: creatine supplementation and exercise. Journal of the International Society of Sports Nutrition, 4, 6. https://doi.org/10.1186/1550-2783-4-6

[290] Williams M. H. (1999). Facts and fallacies of purported ergogenic amino acid supplements. Clinics in sports medicine, 18(3), 633–649. https://doi.org/10.1016/s0278-5919(05)70173-3

[291] Duncan et al (1999) 'PERFORMANCE AND MUSCLE FIBER ADAPTATIONS TO 12 WEEKS OF CREATINE SUPPLEMENTATION AND HEAVY RESISTANCE TRAINING', Medicine & Science in Sports & Exercise: May 1999 - Volume 31 - Issue 5 - p S103.

[292] Olsen, S., Aagaard, P., Kadi, F., Tufekovic, G., Verney, J., Olesen, J. L., Suetta, C., & Kjaer, M. (2006). Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. The Journal of physiology, 573(Pt 2), 525–534. https://doi.org/10.1113/jphysiol.2006.107359

[293] Greenwood, M., Kreider, R., Greenwood, L., Earnest, C. P., Farris, J., Brown, L. E., … Byars, A. (2002). EFFECTS OF CREATINE SUPPLEMENTATION ON THE INCIDENCE OF CRAMPING/INJURY DURING EIGHTEEN WEEKS OF COLLEGIATE BASEBALL TRAINING/COMPETITION. Medicine & Science in Sports & Exercise, 34(5), S146. doi:10.1097/00005768-200205001-00811

[294] Watsford, M. L., Murphy, A., Spinks, W. L., & Walshe, A. D. (2003). Creatine supplementation and its effect on musculotendinous stiffness and performance. Journal of strength and conditioning research, 17(1), 26–33. https://doi.org/10.1519/1533-4287(2003)017<0026:csaieo>2.0.co;2

[295] Kreider R. B. (2003). Effects of creatine supplementation on performance and training adaptations. Molecular and cellular biochemistry, 244(1-2), 89–94.

[296] Greenhaff, P. L., Bodin, K., Soderlund, K., & Hultman, E. (1994). Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. The American journal of physiology, 266(5 Pt 1), E725–E730. https://doi.org/10.1152/ajpendo.1994.266.5.E725

[297] Greenhaff, P., Casey, A., Short, A., Harris, R., Soderlund, K., & Hultman, E. (1993). Influence of oral creatine supplementation of

muscle torque during repeated bouts of maximal voluntary exercise in man. Clinical science, 84 5, 565-71.

[298] Brosnan, J. T., da Silva, R. P., & Brosnan, M. E. (2011). The metabolic burden of creatine synthesis. Amino acids, 40(5), 1325–1331. https://doi.org/10.1007/s00726-011-0853-y

[299] Paddon-Jones, D., Børsheim, E., & Wolfe, R. R. (2004). Potential ergogenic effects of arginine and creatine supplementation. The Journal of nutrition, 134(10 Suppl), 2888S–2895S. https://doi.org/10.1093/jn/134.10.2888s

[300] Greenhaff, P. L. (1997). The nutritional biochemistry of creatine. The Journal of Nutritional Biochemistry, 8(11), 610–618. doi:10.1016/s0955-2863(97)00116-2

[301] Almquist et al (1941) 'CREATINE FORMATION IN THE CHICK', Journal of Biological Chemistry, Volume 141, Issue 2, 1 November 1941, Pages 365-373.

[302] Balsom, P. D., Söderlund, K., & Ekblom, B. (1994). Creatine in humans with special reference to creatine supplementation. Sports medicine (Auckland, N.Z.), 18(4), 268–280. https://doi.org/10.2165/00007256-199418040-00005

[303] Hultman E, Bergstrom J, Spreit L, Soderlund K: Energy metabolism and fatigue. In Biochemistry of Exercise VII Edited by: Taylor A, Gollnick PD, Green H. Human Kinetics: Champaign, IL; 1990:73-92.

[304] Chanutin, A., & Guy, L. P. (1926). THE FATE OF CREATINE WHEN ADMINISTERED TO MAN. Journal of Biological Chemistry, 67(1), 29–41. doi:10.1016/s0021-9258(18)84727-5

[305] Harris, R. C., Söderlund, K., & Hultman, E. (1992). Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clinical Science, 83(3), 367–374. doi:10.1042/cs0830367

[306] Greenhaff, P. L. (1997). The nutritional biochemistry of creatine. The Journal of Nutritional Biochemistry, 8(11), 610–618.

doi:10.1016/s0955-2863(97)00116-2

[307] Hultman, E., Söderlund, K., Timmons, J. A., Cederblad, G., & Greenhaff, P. L. (1996). Muscle creatine loading in men. Journal of applied physiology (Bethesda, Md. : 1985), 81(1), 232–237. https://doi.org/10.1152/jappl.1996.81.1.232

[308] Kaufman, M. J., Prescot, A. P., Ongur, D., Evins, A. E., Barros, T. L., Medeiros, C. L., Covell, J., Wang, L., Fava, M., & Renshaw, P. F. (2009). Oral glycine administration increases brain glycine/creatine ratios in men: a proton magnetic resonance spectroscopy study. Psychiatry research, 173(2), 143–149. https://doi.org/10.1016/j.pscychresns.2009.03.004

[309] Bodansky, M., Duff, V.B., & Hebemann, C.L. (1936). COMPARISON OF GLYCINE AND GUANIDOACETIC ACID AS PRECURSORS OF CREATINE. Journal of Biological Chemistry, 115, 641-652.

[310] Trepanowski, J. F., Farney, T. M., McCarthy, C. G., Schilling, B. K., Craig, S. A., & Bloomer, R. J. (2011). The effects of chronic betaine supplementation on exercise performance, skeletal muscle oxygen saturation and associated biochemical parameters in resistance trained men. Journal of strength and conditioning research, 25(12), 3461–3471. https://doi.org/10.1519/JSC.0b013e318217d48d

[311] Cholewa J.M., Paolone V.J., Wood R., Matthews T. Betaine Supplementation Improves Body Composition And Homocysteine Thiolactone In Strength Trained Men. Med. Sci. Sports Exerc. 2013;45:569

[312] Cholewa, J. M., Hudson, A., Cicholski, T., Cervenka, A., Barreno, K., Broom, K., Barch, M., & Craig, S. (2018). The effects of chronic betaine supplementation on body composition and performance in collegiate females: a double-blind, randomized, placebo controlled trial. Journal of the International Society of Sports Nutrition, 15(1), 37. https://doi.org/10.1186/s12970-018-0243-x

[313] Hoffman, J. R., Ratamess, N. A., Kang, J., Gonzalez, A. M., Beller, N. A., & Craig, S. A. (2011). Effect of 15 days of betaine ingestion on concentric and eccentric force outputs during isokinetic exercise. Journal of strength and conditioning research, 25(8), 2235–2241. https://doi.org/10.1519/JSC.0b013e3182162530

[314] Moro, T., Badiali, F., Fabbri, I., & Paoli, A. (2020). Betaine Supplementation Does Not Improve Muscle Hypertrophy or Strength Following 6 Weeks of Cross-Fit Training. Nutrients, 12(6), 1688. https://doi.org/10.3390/nu12061688

[315] Miller, R. A., Harrison, D. E., Astle, C. M., Bogue, M. A., Brind, J., Fernandez, E., Flurkey, K., Javors, M., Ladiges, W., Leeuwenburgh, C., Macchiarini, F., Nelson, J., Ryazanov, A. G., Snyder, J., Stearns, T. M., Vaughan, D. E., & Strong, R. (2019). Glycine supplementation extends lifespan of male and female mice. Aging cell, 18(3), e12953. https://doi.org/10.1111/acel.12953

[316] Brind, J., Malloy, V., Augie, I., Caliendo, N., Vogelman, J.H., Zimmerman, J.A. and Orentreich, N. (2011), Dietary glycine supplementation mimics lifespan extension by dietary methionine restriction in Fisher 344 rats. The FASEB Journal, 25: 528.2-528.2. https://doi.org/10.1096/fasebj.25.1_supplement.528.2

[317] Obata, F., Miura, M. Enhancing S-adenosyl-methionine catabolism extends Drosophila lifespan. Nat Commun 6, 8332 (2015). https://doi.org/10.1038/ncomms9332

[318] Hashizume, O., Ohnishi, S., Mito, T., Shimizu, A., Ishikawa, K., Nakada, K., Soda, M., Mano, H., Togayachi, S., Miyoshi, H., Okita, K., & Hayashi, J. (2015). Epigenetic regulation of the nuclear-coded GCAT and SHMT2 genes confers human age-associated mitochondrial respiration defects. Scientific reports, 5, 10434. https://doi.org/10.1038/srep10434

[319] Brind, J., Malloy, V., Augie, I., Caliendo, N., Vogelman, J.H., Zimmerman, J.A. and Orentreich, N. (2011), Dietary glycine supplementation mimics lifespan extension by dietary methionine

restriction in Fisher 344 rats. The FASEB Journal, 25: 528.2-528.2. https://doi.org/10.1096/fasebj.25.1_supplement.528.2

[320] Lee, B. C., Kaya, A., & Gladyshev, V. N. (2016). Methionine restriction and life-span control. Annals of the New York Academy of Sciences, 1363, 116–124. https://doi.org/10.1111/nyas.12973

[321] Cavuoto, P., & Fenech, M. F. (2012). A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. Cancer treatment reviews, 38(6), 726–736. https://doi.org/10.1016/j.ctrv.2012.01.004

[322] Oudi, M. E., Aouni, Z., Mazigh, C., Khochkar, R., Gazoueni, E., Haouela, H., & Machghoul, S. (2010). Homocysteine and markers of inflammation in acute coronary syndrome. Experimental and clinical cardiology, 15(2), e25–e28.

[323] Luka, Z., Mudd, S. H., & Wagner, C. (2009). Glycine N-methyltransferase and regulation of S-adenosylmethionine levels. The Journal of biological chemistry, 284(34), 22507–22511. https://doi.org/10.1074/jbc.R109.019273

[324] Fukada (2006). Suppression of methionine-induced hyperhomocysteinemia by glycine and serine in rats. Bioscience, biotechnology, and biochemistry, 70(10), 2403–2409.

[325] Ding et al (2015). Plasma Glycine and Risk of Acute Myocardial Infarction in Patients With Suspected Stable Angina Pectoris. Journal of the American Heart Association, 5(1), e002621.

[326] Chen et al (2012). Deficiency of glycine N-methyltransferase aggravates atherosclerosis in apolipoprotein E-null mice. Molecular medicine (Cambridge, Mass.), 18(1), 744–752.

[327] Martínez-Uña et al (2015). S-Adenosylmethionine increases circulating very-low density lipoprotein clearance in non-alcoholic fatty liver disease. Journal of hepatology, 62(3), 673–681.

[328] Miller, RA, Harrison, DE, Astle, CM, et al. Glycine supplementation extends lifespan of male and female mice. Aging Cell. 2019; 18:e12953. https://doi.org/10.1111/acel.12953

[329] Luka, Z., Mudd, S. H., & Wagner, C. (2009). Glycine N-methyltransferase and regulation of S-adenosylmethionine levels. The Journal of biological chemistry, 284(34), 22507–22511. https://doi.org/10.1074/jbc.R109.019273

[330] McRae M. P. (2013). Betaine supplementation decreases plasma homocysteine in healthy adult participants: a meta-analysis. Journal of chiropractic medicine, 12(1), 20–25. https://doi.org/10.1016/j.jcm.2012.11.001

[331] Reeds, P. J. (2000). Dispensable and Indispensable Amino Acids for Humans. The Journal of Nutrition, 130(7), 1835S–1840S. doi:10.1093/jn/130.7.1835s

[332] Fürst, P., & Stehle, P. (2004). What Are the Essential Elements Needed for the Determination of Amino Acid Requirements in Humans? The Journal of Nutrition, 134(6), 1558S–1565S. doi:10.1093/jn/134.6.1558s

[333] Brosnan JT et al (2007) 'Methionine: A metabolically unique amino acid', Livestock Science, Volume 112, Issues 1–2, October 2007, Pages 2-7.

[334] Finkelstein J. D. (1990). Methionine metabolism in mammals. The Journal of nutritional biochemistry, 1(5), 228–237. https://doi.org/10.1016/0955-2863(90)90070-2

[335] Naghshi, S., Sadeghi, O., Willett, W. C., & Esmaillzadeh, A. (2020). Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ, m2412. https://doi.org/10.1136/bmj.m2412

[336] DiNicolantonio, J. J., & O'Keefe, J. H. (2021). Low-grade metabolic acidosis as a driver of insulin resistance. Open heart, 8(2), e001788. https://doi.org/10.1136/openhrt-2021-001788

[337] DiNicolantonio, J. J., & O'Keefe, J. (2021). Low-grade metabolic acidosis as a driver of chronic disease: a 21st century

public health crisis. Open heart, 8(2), e001730. https://doi.org/10.1136/openhrt-2021-001730

[338] Kapahi, P., Chen, D., Rogers, A. N., Katewa, S. D., Li, P. W., Thomas, E. L., & Kockel, L. (2010). With TOR, less is more: a key role for the conserved nutrient-sensing TOR pathway in aging. Cell metabolism, 11(6), 453–465. https://doi.org/10.1016/j.cmet.2010.05.001

[339] Wolfson, R. L., Chantranupong, L., Saxton, R. A., Shen, K., Scaria, S. M., Cantor, J. R., & Sabatini, D. M. (2016). Sestrin2 is a leucine sensor for the mTORC1 pathway. Science (New York, N.Y.), 351(6268), 43–48. https://doi.org/10.1126/science.aab2674

[340] Powers, R. W., 3rd, Kaeberlein, M., Caldwell, S. D., Kennedy, B. K., & Fields, S. (2006). Extension of chronological life span in yeast by decreased TOR pathway signaling. Genes & development, 20(2), 174–184. https://doi.org/10.1101/gad.1381406

[341] Wu, J. J., Liu, J., Chen, E. B., Wang, J. J., Cao, L., Narayan, N., Fergusson, M. M., Rovira, I. I., Allen, M., Springer, D. A., Lago, C. U., Zhang, S., DuBois, W., Ward, T., deCabo, R., Gavrilova, O., Mock, B., & Finkel, T. (2013). Increased mammalian lifespan and a segmental and tissue-specific slowing of aging after genetic reduction of mTOR expression. Cell reports, 4(5), 913–920. https://doi.org/10.1016/j.celrep.2013.07.030

[342] Jia, K. et al (2004) 'The TOR pathway interacts with the insulin signaling pathway to regulate C. elegans larval development, metabolism and life span', Vol 131, p 3897-3906.

[343] Zoncu, R. et al (2010) 'mTOR: from growth signal integration to cancer, diabetes and ageing', Molecular Cell Biology, Vol 12, p 21-35.

[344] Chano, T. et al (2007) 'RB1CC1 insufficiency causes neuronal atrophy through mTOR signaling alteration and involved in the pathology of Alzheimer's diseases', Vol 1168(7), p 97-105.

[345] Selkoe, DJ. (2008) 'Soluble oligomers of the amyloid β-protein impair synaptic plasticity and behavior', Behavioural Brain

Research, Vol 192(1), p 106-113.

[346] Cellarier, E., Durando, X., Vasson, M. P., Farges, M. C., Demiden, A., Maurizis, J. C., Madelmont, J. C., & Chollet, P. (2003). Methionine dependency and cancer treatment. Cancer treatment reviews, 29(6), 489–499. https://doi.org/10.1016/s0305-7372(03)00118-x

[347] Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., & Szyf, M. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. The Journal of neuroscience : the official journal of the Society for Neuroscience, 25(47), 11045–11054. https://doi.org/10.1523/JNEUROSCI.3652-05.2005

[348] Brind, J., Malloy, V., Augie, I., Caliendo, N., Vogelman, J.H., Zimmerman, J.A. and Orentreich, N. (2011), Dietary glycine supplementation mimics lifespan extension by dietary methionine restriction in Fisher 344 rats. The FASEB Journal, 25: 528.2-528.2. https://doi.org/10.1096/fasebj.25.1_supplement.528.2

[349] Masterjohn 'Balancing Methionine and Glycine in Foods: The Database', Accessed Online November 6th 2022: https://chrismasterjohnphd.com/blog/balancing-methionine-and-glycine-in-foods-the-database

[350] Arnarson (2019) 'Methionine vs. Glycine — Is Too Much Muscle Meat Bad?', Healthline, Accessed Online November 6th 2022: https://www.healthline.com/nutrition/methionine-vs-glycine#what-they-are

[351] Arnarson (2019) 'Methionine vs. Glycine — Is Too Much Muscle Meat Bad?', Healthline, Accessed Online November 6th 2022: https://www.healthline.com/nutrition/methionine-vs-glycine#what-they-are

[352] GUTMAN, G. E., & ALEXANDER, B. (1947). Studies of amino acid metabolism; blood glycine and alanine and their

relationship to the total amino acids in normal subjects. The Journal of biological chemistry, 168(2), 527–536.

[353] Steele et al (1950) 'Amino Acids in the Blood and Urine of Human Subjects Ingesting Different Amounts of the Same Proteins', The Journal of Nutrition, Volume 40, Issue 1, January 1950, Pages 145–158, https://doi.org/10.1093/jn/40.1.145

[354] Kamin, H., & Handler, P. (1951). The metabolism of parenterally administered amino acids. II. Urea synthesis. The Journal of biological chemistry, 188 1, 193-205 .

[355] Bolton, C., & Wright, G. P. (1937). The Absorption of amino acids and their distribution in the body fluids. The Journal of physiology, 89(3), 269–286. https://doi.org/10.1113/jphysiol.1937.sp003477

[356] de Vries, A., Alexander, B., & Quamo, Y. (1948). STUDIES ON AMINO ACID METABOLISM. II. BLOOD GLYCINE AND TOTAL AMINO ACIDS IN VARIOUS PATHOLOGICAL CONDITIONS, WITH OBSERVATIONS ON THE EFFECTS OF INTRAVENOUSLY ADMINISTERED GLYCINE. The Journal of clinical investigation, 27(5), 655–664. https://doi.org/10.1172/JCI102013

[357] Erf, L. A., & Rhoads, C. P. (1940). THE GLYCINE TOLERANCE TEST IN SPRUE AND PERNICIOUS ANEMIA. The Journal of clinical investigation, 19(2), 409–421. https://doi.org/10.1172/JCI101143

[358] Radin et al (1950) 'THE RÔLE OF GLYCINE IN THE BIOSYNTHESIS OF HEME', Journal of Biological Chemistry, Volume 184, Issue 2, 1 June 1950, Pages 745-753.

[359] Whipple, G. H., & Robscheit-Robbins, F. S. (1940). AMINO ACIDS AND HEMOGLOBIN PRODUCTION IN ANEMIA. The Journal of experimental medicine, 71(4), 569–583. https://doi.org/10.1084/jem.71.4.569

[360] CHRISTENSEN, H. N., & LYNCH, E. L. (1948). Decrease of glycine and glutamine in skeletal muscle and of glutamine in liver in

ascorbic acid deficiency in the guinea pig. The Journal of biological chemistry, 172(1), 107–110.

[361] Jackson, A. A., Badaloo, A. V., Forrester, T., Hibbert, J. M., & Persaud, C. (1987). Urinary excretion of 5-oxoproline (pyroglutamic aciduria) as an index of glycine insufficiency in normal man. The British journal of nutrition, 58(2), 207–214. https://doi.org/10.1079/bjn19870088

[362] Nussinovitch, A. (2009). Biopolymer Films and Composite Coatings. Modern Biopolymer Science, 295–326. https://doi.org/10.1016/b978-0-12-374195-0.00010-0

[363] Del Olmo, A., Calzada, J., & Nuñez, M. (2017). Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: Uses, exposure, and controversy. Critical reviews in food science and nutrition, 57(14), 3084–3103. https://doi.org/10.1080/10408398.2015.1087964

[364] Panico, A., Serio, F., Bagordo, F., Grassi, T., Idolo, A., DE Giorgi, M., Guido, M., Congedo, M., & DE Donno, A. (2019). Skin safety and health prevention: an overview of chemicals in cosmetic products. Journal of preventive medicine and hygiene, 60(1), E50–E57. https://doi.org/10.15167/2421-4248/jpmh2019.60.1.1080

[365] Joseph (2018) '6 Potential Health Benefits of Chlorogenic Acid: Coffee's Major Phytonutrient', Nutrition Advance, Accessed Online Nov 26 2022: https://www.nutritionadvance.com/chlorogenic-acid-health-benefits/

[366] Ludwig et al (2014) 'Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking?', Food Funct., 2014, 5, 1718-1726.

[367] John (2011) 'Chlorogenic Acids in Coffee', Healthfully, Accessed Online Nov 26 2022: https://healthfully.com/chlorogenic-acids-in-coffee-7497147.html

[368] Vandevijvere et al (2009) 'Estimate of intake of benzoic acid in the Belgian adult population.' Food Additives & Contaminants: Part A, 26:7, 958-968

[369] Wikipedia (2022) 'Benzoic Acid) 'https://en.wikipedia.org/wiki/Benzoic_acid

[370] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[371] Thomsen A. (1937). THE GLYCINE SYNTHESIS IN PATIENTS WITH PROGRESSIVE MUSCULAR DYSTROPHY. The Journal of clinical investigation, 16(2), 231–236. https://doi.org/10.1172/JCI100852

[372] Pearlman, J. P., & Fielding, R. A. (2006). Creatine monohydrate as a therapeutic aid in muscular dystrophy. Nutrition reviews, 64(2 Pt 1), 80–88. https://doi.org/10.1301/nr.2006.feb.80-88

[373] Aroeira, R. I., Ribeiro, J. A., Sebastião, A. M., & Valente, C. A. (2011). Age-related changes of glycine receptor at the rat hippocampus: from the embryo to the adult. Journal of neurochemistry, 118(3), 339–353. https://doi.org/10.1111/j.1471-4159.2011.07197.x

[374] Persaud, C., Forrester, T., & Jackson, A. A. (1996). Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. The Journal of nutrition, 126(11), 2823–2830. https://doi.org/10.1093/jn/126.11.2823

[375] Jackson A. A. (1991). The glycine story. European journal of clinical nutrition, 45(2), 59–65.

[376] Thomsen A. (1937). THE GLYCINE SYNTHESIS IN PATIENTS WITH PROGRESSIVE MUSCULAR DYSTROPHY. The Journal of clinical investigation, 16(2), 231–236. https://doi.org/10.1172/JCI100852

[377] Jackson A. A. (1991). The glycine story. European journal of clinical nutrition, 45(2), 59–65.

[378] Pflugradt (2022) 'Everything You Need to Know About Benzoic Acid in Food (and if It's Safe)', Accessed Online Nov 26th 2022: https://www.livestrong.com/article/517967-what-foods-contain-benzoic-acid/

[379] Persaud, C., Forrester, T., & Jackson, A. A. (1996). Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. The Journal of nutrition, 126(11), 2823–2830. https://doi.org/10.1093/jn/126.11.2823

[380] Maltby E. J. (1937). Some Observations on Glycine Metabolism in Patients Suffering from Myasthenia Gravis. Canadian Medical Association journal, 36(3), 272–274.

[381] Houck, J.C., de Hesse, C., & Jacob, R.A. (1967). The effect of ageing upon collagen metabolism. Symposia of the Society for Experimental Biology, 21, 403-25 .

[382] Persaud, C., Forrester, T., & Jackson, A. A. (1996). Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. The Journal of nutrition, 126(11), 2823–2830. https://doi.org/10.1093/jn/126.11.2823

[383] Persaud, C., Forrester, T., & Jackson, A. A. (1996). Urinary excretion of 5-L-oxoproline (pyroglutamic acid) is increased during recovery from severe childhood malnutrition and responds to supplemental glycine. The Journal of nutrition, 126(11), 2823–2830. https://doi.org/10.1093/jn/126.11.2823

[384] Meléndez-Hevia, E., De Paz-Lugo, P., Cornish-Bowden, A., & Cárdenas, M. L. (2009). A weak link in metabolism: the metabolic capacity for glycine biosynthesis does not satisfy the need for collagen synthesis. Journal of biosciences, 34(6), 853–872. https://doi.org/10.1007/s12038-009-0100-9

[385] Geiger, M., Li, R. H., & Friess, W. (2003). Collagen sponges for bone regeneration with rhBMP-2. Advanced drug delivery

reviews, 55(12), 1613–1629. https://doi.org/10.1016/j.addr.2003.08.010

[386] Oliveira, S. M., Ringshia, R. A., Legeros, R. Z., Clark, E., Yost, M. J., Terracio, L., & Teixeira, C. C. (2010). An improved collagen scaffold for skeletal regeneration. Journal of biomedical materials research. Part A, 94(2), 371–379. https://doi.org/10.1002/jbm.a.32694

[387] Bunyaratavej, P., & Wang, H. L. (2001). Collagen membranes: a review. Journal of periodontology, 72(2), 215–229. https://doi.org/10.1902/jop.2001.72.2.215

[388] Drury, J. L., & Mooney, D. J. (2003). Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials, 24(24), 4337–4351. https://doi.org/10.1016/s0142-9612(03)00340-5

[389] Tonndorf, R., Aibibu, D., & Cherif, C. (2020). Collagen multifilament spinning. Materials science & engineering. C, Materials for biological applications, 106, 110105. https://doi.org/10.1016/j.msec.2019.110105

[390] Rees SG, Dent CM, Caterson B. Metabolism of proteoglycans in tendon. Scand J Med Sci Sports. 2009 Aug;19(4):470-8. doi: 10.1111/j.1600-0838.2009.00938.x. Epub 2009 Apr 13. PMID: 19422635.

[391] Holm C, Kjaer M, Eliasson P. Achilles tendon rupture--treatment and complications: a systematic review. Scand J Med Sci Sports. 2015 Feb;25(1):e1-10. doi: 10.1111/sms.12209. Epub 2014 Mar 20. PMID: 24650079.

[392] Lieberthal K, Paterson KL, Cook J, Kiss Z, Girdwood M, Bradshaw EJ. Prevalence and factors associated with asymptomatic Achilles tendon pathology in male distance runners. Phys Ther Sport. 2019 Sep;39:64-68. doi: 10.1016/j.ptsp.2019.06.006. Epub 2019 Jun 17. PMID: 31261019.

[393] Lieberthal K, Paterson KL, Cook J, Kiss Z, Girdwood M, Bradshaw EJ. Prevalence and factors associated with asymptomatic

Achilles tendon pathology in male distance runners. Phys Ther Sport. 2019 Sep;39:64-68. doi: 10.1016/j.ptsp.2019.06.006. Epub 2019 Jun 17. PMID: 31261019.

[394] Noback PC, Freibott CE, Tantigate D, et al. Prevalence of Asymptomatic Achilles Tendinosis. Foot & Ankle International. 2018;39(10):1205-1209..

[395] Janssen I, van der Worp H, Hensing S, Zwerver J. Investigating Achilles and patellar tendinopathy prevalence in elite athletics. Res Sports Med. 2018 Jan-Mar;26(1):1-12. doi: 10.1080/15438627.2017.1393748. Epub 2017 Oct 24. PMID: 29064298.

[396] Yasui Y, Tonogai I, Rosenbaum AJ, Shimozono Y, Kawano H, Kennedy JG. The Risk of Achilles Tendon Rupture in the Patients with Achilles Tendinopathy: Healthcare Database Analysis in the United States. Biomed Res Int. 2017;2017:7021862. doi: 10.1155/2017/7021862. Epub 2017 Apr 30. PMID: 28540301; PMCID: PMC5429922.

[397] Egger AC, Berkowitz MJ. Achilles tendon injuries. Curr Rev Musculoskelet Med. 2017 Mar;10(1):72-80. doi: 10.1007/s12178-017-9386-7. PMID: 28194638; PMCID: PMC5344857.

[398] ARNER O, LINDHOLM A, ORELL SR. Histologic changes in subcutaneous rupture of the Achilles tendon; a study of 74 cases. Acta Chir Scand. 1959 May 15;116(5-6):484-90. PMID: 13660717.

[399] Federer AE, Steele JR, Dekker TJ, Liles JL, Adams SB. Tendonitis and Tendinopathy: What Are They and How Do They Evolve? Foot Ankle Clin. 2017 Dec;22(4):665-676. doi: 10.1016/j.fcl.2017.07.002. Epub 2017 Sep 27. PMID: 29078821.

[400] Albers IS, Zwerver J, Diercks RL, Dekker JH, Van den Akker-Scheek I. Incidence and prevalence of lower extremity tendinopathy in a Dutch general practice population: a cross sectional study. BMC Musculoskelet Disord. 2016 Jan 13;17:16. doi: 10.1186/s12891-016-0885-2. PMID: 26759254; PMCID: PMC4711046..

[401] Wilson, J. J., & Best, T. M. (2005). Common overuse tendon problems: A review and recommendations for treatment. American family physician, 72(5), 811–818.

[402] Rolf C, Movin T. Etiology, histopathology, and outcome of surgery in achillodynia. Foot Ankle Int. 1997 Sep;18(9):565-9. doi: 10.1177/107110079701800906. PMID: 9310767.

[403] Praet, S.F.E., et al., Oral Supplementation of Specific Collagen Peptides Combined with Calf-Strengthening Exercises Enhances Function and Reduces Pain in Achilles Tendinopathy Patients. Nutrients, 2019. 11(1).

[404] Shaw G, Lee-Barthel A, Ross ML, Wang B, Baar K. Vitamin C-enriched gelatin supplementation before intermittent activity augments collagen synthesis. Am J Clin Nutr. 2017 Jan;105(1):136-143. doi: 10.3945/ajcn.116.138594. Epub 2016 Nov 16. PMID: 27852613; PMCID: PMC5183725.

[405] Choi FD, Sung CT, Juhasz ML, Mesinkovsk NA. Oral Collagen Supplementation: A Systematic Review of Dermatological Applications. J Drugs Dermatol. 2019 Jan 1;18(1):9-16. PMID: 30681787.

[406] Hexsel D, Zague V, Schunck M, Siega C, Camozzato FO, Oesser S. Oral supplementation with specific bioactive collagen peptides improves nail growth and reduces symptoms of brittle nails. J Cosmet Dermatol. 2017 Dec;16(4):520-526. doi: 10.1111/jocd.12393. Epub 2017 Aug 8. PMID: 28786550.

[407] Sugihara F, Inoue N, Venkateswarathirukumara S. Ingestion of bioactive collagen hydrolysates enhanced pressure ulcer healing in a randomized double-blind placebo-controlled clinical study. Sci Rep. 2018 Jul 30;8(1):11403. doi: 10.1038/s41598-018-29831-7. PMID: 30061579; PMCID: PMC6065362.

[408] Elam ML, Johnson SA, Hooshmand S, Feresin RG, Payton ME, Gu J, Arjmandi BH. A calcium-collagen chelate dietary supplement attenuates bone loss in postmenopausal women with osteopenia: a randomized controlled trial. J Med Food. 2015

Mar;18(3):324-31. doi: 10.1089/jmf.2014.0100. Epub 2014 Oct 14. PMID: 25314004.

[409] Kumar S, Sugihara F, Suzuki K, Inoue N, Venkateswarathirukumara S. A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. J Sci Food Agric. 2015 Mar 15;95(4):702-7. doi: 10.1002/jsfa.6752. Epub 2014 Jun 24. PMID: 24852756.

[410] Martin-Bautista E, Martin-Matillas M, Martin-Lagos JA, Miranda-Leon MT, Muñoz-Torres M, Ruiz-Requena E, Rivero M, Quer J, Puigdueta I, Campoy C. A nutritional intervention study with hydrolyzed collagen in pre-pubertal spanish children: influence on bone modeling biomarkers. J Pediatr Endocrinol Metab. 2011;24(3-4):147-53. doi: 10.1515/jpem.2011.009. PMID: 21648282.

[411] Adam M, Spacek P, Hulejová H, Galiánová A, Blahos J. Postmenopauzální osteoporóza. Lécba kalcitoninem pri dietě bohaté na kolagenní bílkoviny [Postmenopausal osteoporosis. Treatment with calcitonin and a diet rich in collagen proteins]. Cas Lek Cesk. 1996 Jan 31;135(3):74-8. Czech. PMID: 8625373.

[412] Kouguchi, T., Ohmori, T., Shimizu, M., Takahata, Y., Maeyama, Y., Suzuki, T., Morimatsu, F., & Tanabe, S. (2013). Effects of a chicken collagen hydrolysate on the circulation system in subjects with mild hypertension or high-normal blood pressure. Bioscience, biotechnology, and biochemistry, 77(4), 691–696. https://doi.org/10.1271/bbb.120718

[413] Zdzieblik D, Oesser S, Baumstark MW, Gollhofer A, König D. Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. Br J Nutr. 2015 Oct 28;114(8):1237-45. doi: 10.1017/S0007114515002810. Epub 2015 Sep 10. PMID: 26353786; PMCID: PMC4594048.

[414] ElMaraghy AW, Devereaux MW. A systematic review and comprehensive classification of pectoralis major tears. J Shoulder Elbow Surg. 2012 Mar;21(3):412-22. doi: 10.1016/j.jse.2011.04.035. Epub 2011 Aug 10. PMID: 21831661.

[415] Holm C, Kjaer M, Eliasson P. Achilles tendon rupture--treatment and complications: a systematic review. Scand J Med Sci Sports. 2015 Feb;25(1):e1-10. doi: 10.1111/sms.12209. Epub 2014 Mar 20. PMID: 24650079.

[416] Egger AC, Berkowitz MJ. Achilles tendon injuries. Curr Rev Musculoskelet Med. 2017 Mar;10(1):72-80. doi: 10.1007/s12178-017-9386-7. PMID: 28194638; PMCID: PMC5344857.

[417] Lantto I, Heikkinen J, Flinkkilä T, Ohtonen P, Leppilahti J. Epidemiology of Achilles tendon ruptures: increasing incidence over a 33-year period. Scand J Med Sci Sports. 2015 Feb;25(1):e133-8. doi: 10.1111/sms.12253. Epub 2014 May 23. PMID: 24862178.

[418] Houshian S, Tscherning T, Riegels-Nielsen P. The epidemiology of Achilles tendon rupture in a Danish county. Injury. 1998 Nov;29(9):651-4. doi: 10.1016/s0020-1383(98)00147-8. PMID: 10211195.

[419] Magnan B, Bondi M, Pierantoni S, Samaila E. The pathogenesis of Achilles tendinopathy: a systematic review. Foot Ankle Surg. 2014 Sep;20(3):154-9. doi: 10.1016/j.fas.2014.02.010. Epub 2014 Mar 12. PMID: 25103700.

[420] J P, U F, K Q, J O L, P S, K H, M K, H L. Local biochemical and morphological differences in human Achilles tendinopathy: a case control study. BMC Musculoskelet Disord. 2012 Apr 5;13:53. doi: 10.1186/1471-2474-13-53. PMID: 22480275; PMCID: PMC3341204.

[421] Vieira, C. P., De Oliveira, L. P., Da Ré Guerra, F., Dos Santos De Almeida, M., Marcondes, M. C., & Pimentel, E. R. (2015). Glycine improves biochemical and biomechanical properties following inflammation of the achilles tendon. Anatomical record (Hoboken, N.J. : 2007), 298(3), 538–545. https://doi.org/10.1002/ar.23041

[422] March, L., Smith, E. U., Hoy, D. G., Cross, M. J., Sanchez-Riera, L., Blyth, F., Buchbinder, R., Vos, T., & Woolf, A. D. (2014). Burden of disability due to musculoskeletal (MSK) disorders. Best

practice & research. Clinical rheumatology, 28(3), 353–366. https://doi.org/10.1016/j.berh.2014.08.002

[423] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England), 388(10053), 1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6

[424] Hunter, D. J., & Bierma-Zeinstra, S. (2019). Osteoarthritis. Lancet (London, England), 393(10182), 1745–1759. https://doi.org/10.1016/S0140-6736(19)30417-9

[425] CDC (2020) 'A NATIONAL PUBLIC HEALTH AGENDA FOR OSTEOARTHRITIS: 2020 UPDATE', Accessed Online: https://www.cdc.gov/arthritis/docs/oaagenda2020.pdf

[426] Berenbaum F. (2013). Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis and cartilage, 21(1), 16–21. https://doi.org/10.1016/j.joca.2012.11.012

[427] Glyn-Jones, S., Palmer, A. J., Agricola, R., Price, A. J., Vincent, T. L., Weinans, H., & Carr, A. J. (2015). Osteoarthritis. Lancet (London, England), 386(9991), 376–387. https://doi.org/10.1016/S0140-6736(14)60802-3

[428] *https://www.mayoclinic.org/diseases-conditions/osteoarthritis/symptoms-causes/syc-20351925*.

[429] Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol. 2006 Nov;33(11):2271-9. Epub 2006 Oct 1. PMID: 17013996.

[430] Hollander AP, Pidoux I, Reiner A, Rorabeck C, Bourne R, Poole AR. Damage to type II collagen in aging and osteoarthritis starts at the articular surface, originates around chondrocytes, and extends into the cartilage with progressive degeneration. J Clin

Invest. 1995 Dec;96(6):2859-69. doi: 10.1172/JCI118357. PMID: 8675657; PMCID: PMC185997.

[431] García-Coronado, J. M., Martínez-Olvera, L., Elizondo-Omaña, R. E., Acosta-Olivo, C. A., Vilchez-Cavazos, F., Simental-Mendía, L. E., & Simental-Mendía, M. (2019). Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. International orthopaedics, 43(3), 531–538. https://doi.org/10.1007/s00264-018-4211-5

[432] McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., Hawker, G. A., Henrotin, Y., Hunter, D. J., Kawaguchi, H., Kwoh, K., Lohmander, S., Rannou, F., Roos, E. M., & Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis and Cartilage, 22(3), 363–388. https://doi.org/10.1016/j.joca.2014.01.003

[433] Varga, Z., Sabzwari, S., & Vargova, V. (2017). Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. Cureus, 9(4), e1144. https://doi.org/10.7759/cureus.1144

[434] Schink T, Kollhorst B, Varas Lorenzo C, Arfè A, Herings R, Lucchi S, et al. (2018) Risk of ischemic stroke and the use of individual non-steroidal anti-inflammatory drugs: A multi-country European database study within the SOS Project. PLoS ONE 13(9): e0203362.

[435] Sostres, C., Gargallo, C. J., & Lanas, A. (2013). Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis research & therapy, 15 Suppl 3(Suppl 3), S3. https://doi.org/10.1186/ar4175

[436] Wolfe, M. M., Lichtenstein, D. R., & Singh, G. (1999). Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. The New England journal of medicine, 340(24), 1888–1899. https://doi.org/10.1056/NEJM199906173402407

[437] Rahme and Bernatsky (2010) 'NSAIDs and risk of lower gastrointestinal bleeding', The Lancet, VOLUME 376, ISSUE 9736,

P146-148, JULY 17, 2010.

[438] Farid, R., Mirfeizi, Z., Mirheidari, M., Rezaieyazdi, Z., Mansouri, H., Esmaelli, H., Zibadi, S., Rohdewald, P., & Watson, R. R. (2007). Pycnogenol supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis. Nutrition Research, 27(11), 692–697. https://doi.org/10.1016/j.nutres.2007.09.007

[439] Belcaro, G., Cesarone, M. R., Errichi, S., Zulli, C., Errichi, B. M., Vinciguerra, G., Ledda, A., Di Renzo, A., Stuard, S., Dugall, M., Pellegrini, L., Errichi, S., Gizzi, G., Ippolito, E., Ricci, A., Cacchio, M., Cipollone, G., Ruffini, I., Fano, F., Hosoi, M., … Rohdewald, P. (2008). Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. Phytotherapy research : PTR, 22(4), 518–523. https://doi.org/10.1002/ptr.2376

[440] Paultre, K., Cade, W., Hernandez, D., Reynolds, J., Greif, D., & Best, T. M. (2021). Therapeutic effects of turmeric or curcumin extract on pain and function for individuals with knee osteoarthritis: a systematic review. BMJ open sport & exercise medicine, 7(1), e000935. https://doi.org/10.1136/bmjsem-2020-000935

[441] Volpe, Stella Lucia Ph.D., R.D., L.D.N., FACSM. Turmeric and Osteoarthritis. ACSM's Health & Fitness Journal: May/June 2018 - Volume 22 - Issue 3 - p 31-32.

[442] Notarnicola A, Maccagnano G, Moretti L, Pesce V, Tafuri S, Fiore A, Moretti B. Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: Randomized trial. Int J Immunopathol Pharmacol. 2016 Mar;29(1):140-6. doi: 10.1177/0394632015622215. Epub 2015 Dec 18. PMID: 26684635; PMCID: PMC5806735.

[443] Gregori, D., Giacovelli, G., Minto, C., Barbetta, B., Gualtieri, F., Azzolina, D., Vaghi, P., & Rovati, L. C. (2018). Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis.

JAMA, 320(24), 2564–2579. https://doi.org/10.1001/jama.2018.19319

[444] Knapik JJ, Pope R, Hoedebecke SS, Schram B, Orr R, Lieberman HR. Effects of Oral Glucosamine Sulfate on Osteoarthritis-Related Pain and Joint-Space Changes: Systematic Review and Meta-Analysis. J Spec Oper Med. 2018 Winter;18(4):139-147. doi: 10.55460/AUC0-QM7H. PMID: 30566740.

[445] Zhu X, Sang L, Wu D, Rong J, Jiang L. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. J Orthop Surg Res. 2018 Jul 6;13(1):170. doi: 10.1186/s13018-018-0871-5. PMID: 29980200; PMCID: PMC6035477.

[446] Ogata T, Ideno Y, Akai M, Seichi A, Hagino H, Iwaya T, Doi T, Yamada K, Chen AZ, Li Y, Hayashi K. Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. Clin Rheumatol. 2018 Sep;37(9):2479-2487. doi: 10.1007/s10067-018-4106-2. Epub 2018 Apr 30. PMID: 29713967; PMCID: PMC6097075.

[447] Lomonte ABV, Mendonça JA, de Castro Brandão G, Castro ML. Multicenter, randomized, double-blind clinical trial to evaluate efficacy and safety of combined glucosamine sulfate and chondroitin sulfate capsules for treating knee osteoarthritis. Adv Rheumatol. 2018 Dec 5;58(1):41. doi: 10.1186/s42358-018-0041-9. PMID: 30657100.

[448] Simental-Mendía M, Sánchez-García A, Vilchez-Cavazos F, Acosta-Olivo CA, Peña-Martínez VM, Simental-Mendía LE. Effect of glucosamine and chondroitin sulfate in symptomatic knee osteoarthritis: a systematic review and meta-analysis of randomized placebo-controlled trials. Rheumatol Int. 2018 Aug;38(8):1413-1428. doi: 10.1007/s00296-018-4077-2. Epub 2018 Jun 11. PMID: 29947998.

[449] Lubis AMT, Siagian C, Wonggokusuma E, Marsetyo AF, Setyohadi B. Comparison of Glucosamine-Chondroitin Sulfate with

and without Methylsulfonylmethane in Grade I-II Knee Osteoarthritis: A Double Blind Randomized Controlled Trial. Acta Med Indones. 2017 Apr;49(2):105-111. PMID: 28790224.

[450] Debbi, E. M., Agar, G., Fichman, G., Ziv, Y. B., Kardosh, R., Halperin, N., Elbaz, A., Beer, Y., & Debi, R. (2011). Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. BMC complementary and alternative medicine, 11, 50. https://doi.org/10.1186/1472-6882-11-50

[451] Hewlings, S., Kalman, D., & Schneider, L. V. (2019). A Randomized, Double-Blind, Placebo-Controlled, Prospective Clinical Trial Evaluating Water-Soluble Chicken Eggshell Membrane for Improvement in Joint Health in Adults with Knee Osteoarthritis. Journal of medicinal food, 22(9), 875–884. https://doi.org/10.1089/jmf.2019.0068

[452] Truong, T. T. T., Lim, J. M., Cho, H.-R., Kim, Y. S., Dao, D. G., Tran, Q. H., & Choi, J.-S. (2019). A Double-Blind, Randomized Controlled 12-Week Follow-Up Trial to Evaluate the Efficacy and Safety of Polycan in Combination with Glucosamine for the Treatment of Knee Osteoarthritis. Evidence-Based Complementary and Alternative Medicine, 2019, 1–8. https://doi.org/10.1155/2019/9750531

[453] Nash, R. J., Azantsa, B. K., Sharp, H., & Shanmugham, V. (2018). Effectiveness of Cucumis sativus extract versus glucosamine-chondroitin in the management of moderate osteoarthritis: a randomized controlled trial. Clinical interventions in aging, 13, 2119–2126. https://doi.org/10.2147/CIA.S173227

[454] Nieman, D. C., Shanely, R. A., Luo, B., Dew, D., Meaney, M. P., & Sha, W. (2013). A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial. Nutrition journal, 12(1), 154. https://doi.org/10.1186/1475-2891-12-154

[455] Biegert, C., Wagner, I., Lüdtke, R., Kötter, I., Lohmüller, C., Günaydin, I., Taxis, K., & Heide, L. (2004). Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid

arthritis: results of 2 randomized double-blind controlled trials. The Journal of rheumatology, 31(11), 2121–2130.

[456] Schmid, B., Lüdtke, R., Selbmann, H. K., Kötter, I., Tschirdewahn, B., Schaffner, W., & Heide, L. (2001). Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. Phytotherapy research : PTR, 15(4), 344–350. https://doi.org/10.1002/ptr.981

[457] Altman, R. D., & Marcussen, K. C. (2001). Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis and rheumatism, 44(11), 2531–2538. https://doi.org/10.1002/1529-0131(200111)44:11<2531::aid-art433>3.0.co;2-j

[458] Kosuwon, W., Sirichatiwapee, W., Wisanuyotin, T., Jeeravipoolvarn, P., & Laupattarakasem, W. (2010). Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. Journal of the Medical Association of Thailand = Chotmaihet thangphaet, 93(10), 1188–1195.

[459] Nieman, D. C., Shanely, R. A., Luo, B., Dew, D., Meaney, M. P., & Sha, W. (2013). A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial. Nutrition journal, 12(1), 154. https://doi.org/10.1186/1475-2891-12-154

[460] Kumar, S., Sugihara, F., Suzuki, K., Inoue, N., & Venkateswarathirukumara, S. (2014). A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. Journal of the Science of Food and Agriculture, 95(4), 702–707. https://doi.org/10.1002/jsfa.6752

[461] Pereira et al (2016) 'A 30-day clinical investigation of the safety and efficacy of kollaGen II-xs, a new avian sternal collagen type II hydrolysate', HealthMED, Vol 10, Nr 2.

[462] Crowley, D. C., Lau, F. C., Sharma, P., Evans, M., Guthrie, N., Bagchi, M., Bagchi, D., Dey, D. K., & Raychaudhuri, S. P. (2009). Safety and efficacy of undenatured type II collagen in the treatment

of osteoarthritis of the knee: a clinical trial. International journal of medical sciences, 6(6), 312–321. https://doi.org/10.7150/ijms.6.312

[463] Lugo, J. P., Saiyed, Z. M., & Lane, N. E. (2016). Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study. Nutrition journal, 15, 14. https://doi.org/10.1186/s12937-016-0130-8

[464] Bagchi, D., Misner, B., Bagchi, M., Kothari, S. C., Downs, B. W., Fafard, R. D., & Preuss, H. G. (2002). Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. International journal of clinical pharmacology research, 22(3-4), 101–110.

[465] Kiers, J. L., & Bult, J. (2021). Mildly Processed Natural Eggshell Membrane Alleviates Joint Pain Associated with Osteoarthritis of the Knee: A Randomized Double-Blind Placebo-Controlled Study. Journal of medicinal food, 24(3), 292–298. https://doi.org/10.1089/jmf.2020.0034

[466] Hewlings, S., Kalman, D., & Schneider, L. V. (2019). A Randomized, Double-Blind, Placebo-Controlled, Prospective Clinical Trial Evaluating Water-Soluble Chicken Eggshell Membrane for Improvement in Joint Health in Adults with Knee Osteoarthritis. Journal of medicinal food, 22(9), 875–884. https://doi.org/10.1089/jmf.2019.0068

[467] Ruff, K. J., Winkler, A., Jackson, R. W., DeVore, D. P., & Ritz, B. W. (2009). Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study. Clinical rheumatology, 28(8), 907–914. https://doi.org/10.1007/s10067-009-1173-4

[468] Ruff, K. J., DeVore, D. P., Leu, M. D., & Robinson, M. A. (2009). Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. Clinical interventions in aging, 4, 235–240. https://doi.org/10.2147/cia.s5797

[469] Ruff, K. J., Morrison, D., Duncan, S. A., Back, M., Aydogan, C., & Theodosakis, J. (2018). Beneficial effects of natural eggshell membrane versus placebo in exercise-induced joint pain, stiffness, and cartilage turnover in healthy, postmenopausal women. Clinical interventions in aging, 13, 285–295. https://doi.org/10.2147/CIA.S153782

[470] Iwai, K., Hasegawa, T., Taguchi, Y., Morimatsu, F., Sato, K., Nakamura, Y., Higashi, A., Kido, Y., Nakabo, Y., & Ohtsuki, K. (2005). Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates. Journal of agricultural and food chemistry, 53(16), 6531–6536. https://doi.org/10.1021/jf050206p

[471] Skov, K., Oxfeldt, M., Thøgersen, R., Hansen, M., & Bertram, H. C. (2019). Enzymatic Hydrolysis of a Collagen Hydrolysate Enhances Postprandial Absorption Rate-A Randomized Controlled Trial. Nutrients, 11(5), 1064. https://doi.org/10.3390/nu11051064

[472] MATSUDA, N., KOYAMA, Y., HOSAKA, Y., UEDA, H., WATANABE, T., ARAYA, T., IRIE, S., & TAKEHANA, K. (2006). Effects of Ingestion of Collagen Peptide on Collagen Fibrils and Glycosaminoglycans in the Dermis. Journal of Nutritional Science and Vitaminology, 52(3), 211–215. https://doi.org/10.3177/jnsv.52.211

[473] McAlindon, T. E., Nuite, M., Krishnan, N., Ruthazer, R., Price, L. L., Burstein, D., Griffith, J., & Flechsenhar, K. (2011). Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. Osteoarthritis and cartilage, 19(4), 399–405. https://doi.org/10.1016/j.joca.2011.01.001

[474] Zdzieblik, D., Oesser, S., Gollhofer, A., & König, D. (2017). Improvement of activity-related knee joint discomfort following supplementation of specific collagen peptides. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme, 42(6), 588–595. https://doi.org/10.1139/apnm-2016-0390

[475] Benito-Ruiz, P., Camacho-Zambrano, M. M., Carrillo-Arcentales, J. N., Mestanza-Peralta, M. A., Vallejo-Flores, C. A., Vargas-López, S. V., Villacís-Tamayo, R. A., & Zurita-Gavilanes, L. A. (2009). A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. International journal of food sciences and nutrition, 60 Suppl 2, 99–113. https://doi.org/10.1080/09637480802498820

[476] Moskowitz R. W. (2000). Role of collagen hydrolysate in bone and joint disease. Seminars in arthritis and rheumatism, 30(2), 87–99. https://doi.org/10.1053/sarh.2000.9622

[477] Kumar, S., Sugihara, F., Suzuki, K., Inoue, N., & Venkateswarathirukumara, S. (2014). A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. Journal of the Science of Food and Agriculture, 95(4), 702–707. https://doi.org/10.1002/jsfa.6752

[478] Oesser, S., Adam, M., Babel, W., & Seifert, J. (1999). Oral administration of (14)C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). The Journal of nutrition, 129(10), 1891–1895. https://doi.org/10.1093/jn/129.10.1891

[479] Oesser, S., & Seifert, J. (2003). Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell and tissue research, 311(3), 393–399. https://doi.org/10.1007/s00441-003-0702-8

[480] Shigemura, Y., Iwai, K., Morimatsu, F., Iwamoto, T., Mori, T., Oda, C., Taira, T., Park, E. Y., Nakamura, Y., & Sato, K. (2009). Effect of Prolyl-hydroxyproline (Pro-Hyp), a food-derived collagen peptide in human blood, on growth of fibroblasts from mouse skin. Journal of agricultural and food chemistry, 57(2), 444–449. https://doi.org/10.1021/jf802785h

[481] Postlethwaite AE, Seyer JM, Kang AH. Chemotactic attraction of human fibroblasts to type I, II, and III collagens and collagen-derived peptides. Proc Natl Acad Sci U S A. 1978

Feb;75(2):871-5. doi: 10.1073/pnas.75.2.871. PMID: 204938; PMCID: PMC411359.

[482] Jerger, S., Centner, C., Lauber, B., Seynnes, O., Sohnius, T., Jendricke, P., Oesser, S., Gollhofer, A., & König, D. (2022). Effects of specific collagen peptide supplementation combined with resistance training on Achilles tendon properties. Scandinavian journal of medicine & science in sports, 32(7), 1131–1141. https://doi.org/10.1111/sms.14164

[483] Bagchi, D., Misner, B., Bagchi, M., Kothari, S. C., Downs, B. W., Fafard, R. D., & Preuss, H. G. (2002). Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. International journal of clinical pharmacology research, 22(3-4), 101–110.

[484] Orhan, C., Juturu, V., Sahin, E., Tuzcu, M., Ozercan, I. H., Durmus, A. S., Sahin, N., & Sahin, K. (2021). Undenatured Type II Collagen Ameliorates Inflammatory Responses and Articular Cartilage Damage in the Rat Model of Osteoarthritis. Frontiers in Veterinary Science, 8. https://doi.org/10.3389/fvets.2021.617789

[485] Barnett, M. L., Kremer, J. M., St Clair, E. W., Clegg, D. O., Furst, D., Weisman, M., Fletcher, M. J., Chasan-Taber, S., Finger, E., Morales, A., Le, C. H., & Trentham, D. E. (1998). Treatment of rheumatoid arthritis with oral type II collagen. Results of a multicenter, double-blind, placebo-controlled trial. Arthritis and rheumatism, 41(2), 290–297. https://doi.org/10.1002/1529-0131(199802)41:2<290::AID-ART13>3.0.CO;2-R

[486] Bagchi, D., Misner, B., Bagchi, M., Kothari, S. C., Downs, B. W., Fafard, R. D., & Preuss, H. G. (2002). Effects of orally administered undenatured type II collagen against arthritic inflammatory diseases: a mechanistic exploration. International journal of clinical pharmacology research, 22(3-4), 101–110.

[487] Trentham, D. E., Dynesius-Trentham, R. A., Orav, E. J., Combitchi, D., Lorenzo, C., Sewell, K. L., Hafler, D. A., & Weiner, H. L. (1993). Effects of oral administration of type II collagen on

rheumatoid arthritis. Science (New York, N.Y.), 261(5129), 1727–1730. https://doi.org/10.1126/science.8378772

[488] Crowley, D. C., Lau, F. C., Sharma, P., Evans, M., Guthrie, N., Bagchi, M., Bagchi, D., Dey, D. K., & Raychaudhuri, S. P. (2009). Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. International Journal of Medical Sciences, 312–321. https://doi.org/10.7150/ijms.6.312

[489] van der Kraan, P. M., Vitters, E. L., de Vries, B. J., & van den Berg, W. B. (1990). High susceptibility of human articular cartilage glycosaminoglycan synthesis to changes in inorganic sulfate availability. Journal of orthopaedic research : official publication of the Orthopaedic Research Society, 8(4), 565–571. https://doi.org/10.1002/jor.1100080413

[490] DeAngelis, P.L. (2002), Evolution of glycosaminoglycans and their glycosyltransferases: Implications for the extracellular matrices of animals and the capsules of pathogenic bacteria. Anat. Rec., 268: 317-326. https://doi.org/10.1002/ar.10163

[491] Esko, Jeffrey D; Kimata, Koji; Lindahl, Ulf (2009). "Chapter 16: Proteoglycans and Sulfated Glycosaminoglycans". Essentials of Glycobiology. Cold Spring Harbor Laboratory Press. ISBN 978-0879695590.

[492] Nunes, R. M., Girão, V., Cunha, P., Feitosa, J., Pinto, A., & Rocha, F. (2021). Decreased Sulfate Content and Zeta Potential Distinguish Glycosaminoglycans of the Extracellular Matrix of Osteoarthritis Cartilage. Frontiers in medicine, 8, 612370. https://doi.org/10.3389/fmed.2021.612370

[493] McAlindon, T. E., LaValley, M. P., Gulin, J. P., & Felson, D. T. (2000). Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA, 283(11), 1469–1475. https://doi.org/10.1001/jama.283.11.1469

[494] Roos, E. M., & Dahlberg, L. (2005). Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of

osteoarthritis. Arthritis and rheumatism, 52(11), 3507–3514. https://doi.org/10.1002/art.21415

[495] Mark F. McCarty, James H. O'Keefe & James J. DiNicolantonio (2019) Glucosamine for the Treatment of Osteoarthritis: The Time Has Come for Higher-Dose Trials, Journal of Dietary Supplements, 16:2, 179-192, DOI: 10.1080/19390211.2018.1448920

[496] Mark F. McCarty, James H. O'Keefe & James J. DiNicolantonio (2019) Glucosamine for the Treatment of Osteoarthritis: The Time Has Come for Higher-Dose Trials, Journal of Dietary Supplements, 16:2, 179-192, DOI: 10.1080/19390211.2018.1448920

[497] McCarty, M. F., O'Keefe, J. H., & DiNicolantonio, J. J. (2019). Glucosamine for the Treatment of Osteoarthritis: The Time Has Come for Higher-Dose Trials. Journal of dietary supplements, 16(2), 179–192. https://doi.org/10.1080/19390211.2018.1448920

[498] Esfandiari, H., Pakravan, M., Zakeri, Z., Ziaie, S., Pakravan, P., & Ownagh, V. (2017). Effect of glucosamine on intraocular pressure: a randomized clinical trial. Eye (London, England), 31(3), 389–394. https://doi.org/10.1038/eye.2016.221

[499] Yuenyongviwat, V., Kiddee, W., & Tangtrakulwanich, B. (2019). Effect of glucosamine sulfate on intraocular pressure in patients with knee osteoarthritis: A prospective randomized controlled trial. Journal francais d'ophtalmologie, 42(7), 711–715. https://doi.org/10.1016/j.jfo.2019.03.005

[500] King, D. E., & Xiang, J. (2020). Glucosamine/Chondroitin and Mortality in a US NHANES Cohort. The Journal of the American Board of Family Medicine, 33(6), 842–847. doi:10.3122/jabfm.2020.06.200110

[501] Ma, H., Li, X., Sun, D., Zhou, T., Ley, S. H., Gustat, J., … Qi, L. (2019). Association of habitual glucosamine use with risk of cardiovascular disease: prospective study in UK Biobank. BMJ, l1628. doi:10.1136/bmj.l1628

[502] Baker D. H. (1986). Utilization of isomers and analogs of amino acids and other sulfur-containing compounds. Progress in food & nutrition science, 10(1-2), 133–178.

[503] Bianchini, F., & Vainio, H. (2001). Allium vegetables and organosulfur compounds: do they help prevent cancer?. Environmental health perspectives, 109(9), 893–902. https://doi.org/10.1289/ehp.01109893

[504] Sparnins, V. L., Barany, G., & Wattenberg, L. W. (1988). Effects of organosulfur compounds from garlic and onions on benzo[a]pyrene-induced neoplasia and glutathione S-transferase activity in the mouse. Carcinogenesis, 9(1), 131–134. https://doi.org/10.1093/carcin/9.1.131

[505] Grimble R. F. (2006). The effects of sulfur amino acid intake on immune function in humans. The Journal of nutrition, 136(6 Suppl), 1660S–1665S. https://doi.org/10.1093/jn/136.6.1660S

[506] Kleinman, W. A., & Richie, J. P., Jr (2000). Status of glutathione and other thiols and disulfides in human plasma. Biochemical pharmacology, 60(1), 19–29. https://doi.org/10.1016/s0006-2952(00)00293-8

[507] Moore, L. E., Brennan, P., Karami, S., Hung, R. J., Hsu, C., Boffetta, P., Toro, J., Zaridze, D., Janout, V., Bencko, V., Navratilova, M., Szeszenia-Dabrowska, N., Mates, D., Mukeria, A., Holcatova, I., Welch, R., Chanock, S., Rothman, N., & Chow, W. H. (2007). Glutathione S-transferase polymorphisms, cruciferous vegetable intake and cancer risk in the Central and Eastern European Kidney Cancer Study. Carcinogenesis, 28(9), 1960–1964. https://doi.org/10.1093/carcin/bgm151

[508] Bahadoran, Z., Mirmiran, P., Hosseinpanah, F., Hedayati, M., Hosseinpour-Niazi, S., & Azizi, F. (2011). Broccoli sprouts reduce oxidative stress in type 2 diabetes: a randomized double-blind clinical trial. European journal of clinical nutrition, 65(8), 972–977. https://doi.org/10.1038/ejcn.2011.59

[509] Nieman, D. C., Shanely, R. A., Luo, B., Dew, D., Meaney, M. P., & Sha, W. (2013). A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial. Nutrition journal, 12(1), 154. https://doi.org/10.1186/1475-2891-12-154

[510] Rohdewald P. (2002). A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. International journal of clinical pharmacology and therapeutics, 40(4), 158–168. https://doi.org/10.5414/cpp40158

[511] Rohdewald P. (2002). A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. International journal of clinical pharmacology and therapeutics, 40(4), 158–168. https://doi.org/10.5414/cpp40158

[512] Devaraj, S., Vega-López, S., Kaul, N., Schönlau, F., Rohdewald, P., & Jialal, I. (2002). Supplementation with a pine bark extract rich in polyphenols increases plasma antioxidant capacity and alters the plasma lipoprotein profile. Lipids, 37(10), 931–934. https://doi.org/10.1007/s11745-006-0982-3

[513] Rohdewald, P.J. (2019). Pleiotropic Effects of French Maritime Pine Bark Extract to Promote Healthy Aging. Rejuvenation research, 22 3, 210-217 .

[514] Koch R. (2002). Comparative study of Venostasin and Pycnogenol in chronic venous insufficiency. Phytotherapy research : PTR, 16 Suppl 1, S1–S5. https://doi.org/10.1002/ptr.1010

[515] Cesarone, M. R., Belcaro, G., Rohdewald, P., Pellegrini, L., Ledda, A., Vinciguerra, G., Ricci, A., Gizzi, G., Ippolito, E., Fano, F., Dugall, M., Acerbi, G., Cacchio, M., Di Renzo, A., Hosoi, M., Stuard, S., & Corsi, M. (2006). Comparison of Pycnogenol and Daflon in treating chronic venous insufficiency: a prospective, controlled study. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis, 12(2), 205–212. https://doi.org/10.1177/1076029606012002 09

[516] Liu, X., Zhou, H. J., & Rohdewald, P. (2004). French maritime pine bark extract Pycnogenol dose-dependently lowers glucose in type 2 diabetic patients. Diabetes care, 27(3), 839. https://doi.org/10.2337/diacare.27.3.839

[517] Zibadi, S., Rohdewald, P. J., Park, D., & Watson, R. R. (2008). Reduction of cardiovascular risk factors in subjects with type 2 diabetes by Pycnogenol supplementation. Nutrition research (New York, N.Y.), 28(5), 315–320. https://doi.org/10.1016/j.nutres.2008.03.003

[518] Rohdewald P. (2002). A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. International journal of clinical pharmacology and therapeutics, 40(4), 158–168. https://doi.org/10.5414/cpp40158

[519] Grether-Beck et al (2016) 'French Maritime Pine Bark Extract (Pycnogenol®) Effects on Human Skin: Clinical and Molecular Evidence', Skin Pharmacol Physiol 2016;29:13-17.

[520] Sime, S., & Reeve, V. E. (2004). Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol. Photochemistry and photobiology, 79(2), 193–198. https://doi.org/10.1562/0031-8655(2004)079<0193:pfiiac>2.0.co;2

[521] Nishioka, K., Hidaka, T., Nakamura, S., Umemura, T., Jitsuiki, D., Soga, J., Goto, C., Chayama, K., Yoshizumi, M., & Higashi, Y. (2007). Pycnogenol, French maritime pine bark extract, augments endothelium-dependent vasodilation in humans. Hypertension research : official journal of the Japanese Society of Hypertension, 30(9), 775–780. https://doi.org/10.1291/hypres.30.775

[522] Rohdewald P. (2002). A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. International journal of clinical pharmacology and therapeutics, 40(4), 158–168. https://doi.org/10.5414/cpp40158

[523] Belcaro, G., Cornelli, U., Luzzi, R., Cesarone, M. R., Dugall, M., Feragalli, B., Errichi, S., Ippolito, E., Grossi, M. G., Hosoi, M.,

Cornelli, M., & Gizzi, G. (2013). Pycnogenol® supplementation improves health risk factors in subjects with metabolic syndrome. Phytotherapy research : PTR, 27(10), 1572–1578. https://doi.org/10.1002/ptr.4883

[524] Gulati O. P. (2014). Pycnogenol® in chronic venous insufficiency and related venous disorders. Phytotherapy research : PTR, 28(3), 348–362. https://doi.org/10.1002/ptr.5019

[525] Belcaro, G., Dugall, M., Luzzi, R., Ippolito, E., & Cesarone, M. R. (2017). Postpartum Varicose Veins: Supplementation with Pycnogenol or Elastic Compression-A 12-Month Follow-Up. The International journal of angiology : official publication of the International College of Angiology, Inc, 26(1), 12–19. https://doi.org/10.1055/s-0033-1363784

[526] Ledda, A., Belcaro, G., Feragalli, B., Cornelli, U., Dugall, M., Corsi, M., & Cesarone, M. R. (2018). Benign prostatic hypertrophy: Pycnogenol® supplementation improves prostate symptoms and residual bladder volume. Minerva medica, 109(4), 280–284. https://doi.org/10.23736/S0026-4806.18.05572-6

[527] Hosoi, M., Belcaro, G., Saggino, A., Luzzi, R., Dugall, M., & Feragalli, B. (2018). Pycnogenol® supplementation in minimal cognitive dysfunction. Journal of neurosurgical sciences, 62(3), 279–284. https://doi.org/10.23736/S0390-5616.18.04382-5

[528] Belcaro, G., Dugall, M., Ippolito, E., Hu, S., Saggino, A., & Feragalli, B. (2015). The COFU3 Study. Improvement in cognitive function, attention, mental performance with Pycnogenol® in healthy subjects (55-70) with high oxidative stress. Journal of neurosurgical sciences, 59(4), 437–446.

[529] Belcaro, G., Luzzi, R., Dugall, M., Ippolito, E., & Saggino, A. (2014). Pycnogenol® improves cognitive function, attention, mental performance and specific professional skills in healthy professionals aged 35-55. Journal of neurosurgical sciences, 58(4), 239–248.

[530] Luzzi, R., Belcaro, G., Zulli, C., Cesarone, M. R., Cornelli, U., Dugall, M., Hosoi, M., & Feragalli, B. (2011). Pycnogenol®

supplementation improves cognitive function, attention and mental performance in students. Panminerva medica, 53(3 Suppl 1), 75–82.

[531] Ryan, J., Croft, K., Mori, T., Wesnes, K., Spong, J., Downey, L., Kure, C., Lloyd, J., & Stough, C. (2008). An examination of the effects of the antioxidant Pycnogenol on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. Journal of psychopharmacology (Oxford, England), 22(5), 553–562. https://doi.org/10.1177/0269881108091584

[532] Ross S. M. (2016). Allergic Rhinitis: A Proprietary Extract of Pinus pinaster Aiton (Pycnogenol) Is Found to Improve the Symptoms Associated With Allergic Rhinitis. Holistic nursing practice, 30(5), 301–304. https://doi.org/10.1097/HNP.0000000000000170

[533] Belcaro, G., Luzzi, R., Cesinaro Di Rocco, P., Cesarone, M. R., Dugall, M., Feragalli, B., Errichi, B. M., Ippolito, E., Grossi, M. G., Hosoi, M., Errichi, S., Cornelli, U., Ledda, A., & Gizzi, G. (2011). Pycnogenol® improvements in asthma management. Panminerva medica, 53(3 Suppl 1), 57–64.

[534] Belcaro, G., Cesarone, M. R., Errichi, S., Zulli, C., Errichi, B. M., Vinciguerra, G., Ledda, A., Di Renzo, A., Stuard, S., Dugall, M., Pellegrini, L., Errichi, S., Gizzi, G., Ippolito, E., Ricci, A., Cacchio, M., Cipollone, G., Ruffini, I., Fano, F., Hosoi, M., … Rohdewald, P. (2008). Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. Phytotherapy research : PTR, 22(4), 518–523. https://doi.org/10.1002/ptr.2376

[535] Cisár, P., Jány, R., Waczulíková, I., Sumegová, K., Muchová, J., Vojtassák, J., Duračková, Z., Lisý, M., & Rohdewald, P. (2008). Effect of pine bark extract (Pycnogenol) on symptoms of knee osteoarthritis. Phytotherapy research : PTR, 22(8), 1087–1092. https://doi.org/10.1002/ptr.2461

[536] Mülek, M., Seefried, L., Genest, F., & Högger, P. (2017). Distribution of Constituents and Metabolites of Maritime Pine Bark

Extract (Pycnogenol®) into Serum, Blood Cells, and Synovial Fluid of Patients with Severe Osteoarthritis: A Randomized Controlled Trial. Nutrients, 9(5), 443. https://doi.org/10.3390/nu9050443

[537] Belcaro, G., Cesarone, M. R., Errichi, S., Zulli, C., Errichi, B. M., Vinciguerra, G., Ledda, A., Di Renzo, A., Stuard, S., Dugall, M., Pellegrini, L., Gizzi, G., Ippolito, E., Ricci, A., Cacchio, M., Cipollone, G., Ruffini, I., Fano, F., Hosoi, M., & Rohdewald, P. (2008). Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol. Redox report : communications in free radical research, 13(6), 271–276. https://doi.org/10.1179/135100008X309019

[538] Grimm, T., Chovanová, Z., Muchová, J. et al. Inhibition of NF-κB activation and MMP-9 secretion by plasma of human volunteers after ingestion of maritime pine bark extract (Pycnogenol). J Inflamm 3, 1 (2006). https://doi.org/10.1186/1476-9255-3-1

[539] Jessberger, S., Högger, P., Genest, F., Salter, D. M., & Seefried, L. (2017). Cellular pharmacodynamic effects of Pycnogenol® in patients with severe osteoarthritis: a randomized controlled pilot study. BMC complementary and alternative medicine, 17(1), 537. https://doi.org/10.1186/s12906-017-2044-1

[540] Belcaro, G., Cesarone, M. R., Errichi, S., Zulli, C., Errichi, B. M., Vinciguerra, G., Ledda, A., Di Renzo, A., Stuard, S., Dugall, M., Pellegrini, L., Errichi, S., Gizzi, G., Ippolito, E., Ricci, A., Cacchio, M., Cipollone, G., Ruffini, I., Fano, F., Hosoi, M., … Rohdewald, P. (2008). Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. Phytotherapy research : PTR, 22(4), 518–523. https://doi.org/10.1002/ptr.2376

[541] Cisár, P., Jány, R., Waczulíková, I., Sumegová, K., Muchová, J., Vojtassák, J., Duračková, Z., Lisý, M., & Rohdewald, P. (2008). Effect of pine bark extract (Pycnogenol) on symptoms of knee osteoarthritis. Phytotherapy research : PTR, 22(8), 1087–1092. https://doi.org/10.1002/ptr.2461

[542] Farid, R., Mirfeizi, Z., Mirheidari, M., Rezaieyazdi, Z., Mansouri, H., Esmaelli, H., Zibadi, S., Rohdewald, P., & Watson, R. R. (2007). Pycnogenol supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis. Nutrition Research, 27(11), 692–697. https://doi.org/10.1016/j.nutres.2007.09.007

[543] Sood, S., & Nagpal, M. (2013). Role of curcumin in systemic and oral health: An overview. Journal of Natural Science, Biology and Medicine, 4(1), 3. doi:10.4103/0976-9668.107253

[544] Derosa, G., Maffioli, P., Simental-Mendía, L. E., Bo, S., & Sahebkar, A. (2016). Effect of curcumin on circulating interleukin-6 concentrations: A systematic review and meta-analysis of randomized controlled trials. Pharmacological research, 111, 394–404. https://doi.org/10.1016/j.phrs.2016.07.004

[545] Sahebkar, A., Cicero, A., Simental-Mendía, L. E., Aggarwal, B. B., & Gupta, S. C. (2016). Curcumin downregulates human tumor necrosis factor-α levels: A systematic review and meta-analysis ofrandomized controlled trials. Pharmacological research, 107, 234–242. https://doi.org/10.1016/j.phrs.2016.03.026

[546] Panahi, Y., Hosseini, M. S., Khalili, N., Naimi, E., Majeed, M., & Sahebkar, A. (2015). Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clinical nutrition (Edinburgh, Scotland), 34(6), 1101–1108. https://doi.org/10.1016/j.clnu.2014.12.019

[547] Srivastava, S., Saksena, A. K., Khattri, S., Kumar, S., & Dagur, R. S. (2016). Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. Inflammopharmacology, 24(6), 377–388. https://doi.org/10.1007/s10787-016-0289-9

[548] Panahi, Y., Alishiri, G. H., Parvin, S., & Sahebkar, A. (2016). Mitigation of Systemic Oxidative Stress by Curcuminoids in

Osteoarthritis: Results of a Randomized Controlled Trial. Journal of dietary supplements, 13(2), 209–220. https://doi.org/10.3109/19390211.2015.1008611

[549] Madhu, K., Chanda, K., & Saji, M. J. (2013). Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. Inflammopharmacology, 21(2), 129–136. https://doi.org/10.1007/s10787-012-0163-3

[550] Kuptniratsaikul, V., Thanakhumtorn, S., Chinswangwatanakul, P., Wattanamongkonsil, L., & Thamlikitkul, V. (2009). Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. Journal of alternative and complementary medicine (New York, N.Y.), 15(8), 891–897. https://doi.org/10.1089/acm.2008.0186

[551] Kuptniratsaikul, V., Dajpratham, P., Taechaarpornkul, W., Buntragulpoontawee, M., Lukkanapichonchut, P., Chootip, C., Saengsuwan, J., Tantayakom, K., & Laongpech, S. (2014). Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clinical interventions in aging, 9, 451–458. https://doi.org/10.2147/CIA.S58535

[552] Kizhakkedath R. (2013). Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis. Molecular medicine reports, 8(5), 1542–1548. https://doi.org/10.3892/mmr.2013.1661

[553] Tayyem et al (2006). Curcumin Content of Turmeric and Curry Powders. Nutrition and Cancer, 55(2), 126–131. doi:10.1207/s15327914nc5502_2

[554] Sharma, R. A., Gescher, A. J., & Steward, W. P. (2005). Curcumin: The story so far. European Journal of Cancer, 41(13), 1955–1968. doi:10.1016/j.ejca.2005.05.009

[555] Shoba et al (1998). Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. Planta Medica, 64(04), 353–356. doi:10.1055/s-2006-957450

[556] Myers, B. M., Smith, J. L., & Graham, D. Y. (1987). Effect of red pepper and black pepper on the stomach. The American journal of gastroenterology, 82(3), 211–214.

[557] Aggarwal, B. B., Yuan, W., Li, S., & Gupta, S. C. (2013). Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. Molecular nutrition & food research, 57(9), 1529–1542. https://doi.org/10.1002/mnfr.201200838

[558] Aggarwal, B. B., Yuan, W., Li, S., & Gupta, S. C. (2013). Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. Molecular nutrition & food research, 57(9), 1529–1542. https://doi.org/10.1002/mnfr.201200838

[559] Madhu, K., Chanda, K., & Saji, M. J. (2013). Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. Inflammopharmacology, 21(2), 129–136. https://doi.org/10.1007/s10787-012-0163-3

[560] Wang, Z., Jones, G., Winzenberg, T., Cai, G., Laslett, L. L., Aitken, D., Hopper, I., Singh, A., Jones, R., Fripp, J., Ding, C., & Antony, B. (2020). Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion-Synovitis of Knee Osteoarthritis : A Randomized Trial. Annals of internal medicine, 173(11), 861–869. https://doi.org/10.7326/M20-0990

[561] Calderón-Pérez, L., Llauradó, E., Companys, J., Pla-Pagà, L., Boqué, N., Puiggrós, F., Valls, R.-M., Pedret, A., Llabrés, J. M., Arola, L., & Solà, R. (2021). Acute Effects of Turmeric Extracts on

Knee Joint Pain: A Pilot, Randomized Controlled Trial. Journal of Medicinal Food, 24(4), 436–440. https://doi.org/10.1089/jmf.2020.0074

[562] Raj, J. P., Venkatachalam, S., Racha, P., Bhaskaran, S., & Amaravati, R. S. (2020). Effect of Turmacin supplementation on joint discomfort and functional outcome among healthy participants - A randomized placebo-controlled trial. Complementary therapies in medicine, 53, 102522. https://doi.org/10.1016/j.ctim.2020.102522

[563] Debbi, E. M., Agar, G., Fichman, G., Ziv, Y. B., Kardosh, R., Halperin, N., Elbaz, A., Beer, Y., & Debi, R. (2011). Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. BMC complementary and alternative medicine, 11, 50. https://doi.org/10.1186/1472-6882-11-50

[564] Morton, J. I., & Siegel, B. V. (1986). Effects of oral dimethyl sulfoxide and dimethyl sulfone on murine autoimmune lymphoproliferative disease. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.), 183(2), 227–230. https://doi.org/10.3181/00379727-183-42409

[565] Debbi, E. M., Agar, G., Fichman, G., Ziv, Y. B., Kardosh, R., Halperin, N., Elbaz, A., Beer, Y., & Debi, R. (2011). Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. BMC complementary and alternative medicine, 11, 50. https://doi.org/10.1186/1472-6882-11-50

[566] Brien, S., Prescott, P., Bashir, N., Lewith, H., & Lewith, G. (2008). Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. Osteoarthritis and cartilage, 16(11), 1277–1288. https://doi.org/10.1016/j.joca.2008.03.002

[567] Usha, P. R., & Naidu, M. U. (2004). Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and their Combination in Osteoarthritis. Clinical drug investigation, 24(6), 353–363. https://doi.org/10.2165/00044011-200424060-00005

[568] Kim, L. S., Axelrod, L. J., Howard, P., Buratovich, N., & Waters, R. F. (2006). Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. Osteoarthritis and cartilage, 14(3), 286–294. https://doi.org/10.1016/j.joca.2005.10.003

[569] Debbi, E. M., Agar, G., Fichman, G., Ziv, Y. B., Kardosh, R., Halperin, N., Elbaz, A., Beer, Y., & Debi, R. (2011). Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. BMC complementary and alternative medicine, 11, 50. https://doi.org/10.1186/1472-6882-11-50

[570] Maroudas A. I. (1976). Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature, 260(5554), 808–809. https://doi.org/10.1038/260808a0

[571] Venn, M., & Maroudas, A. (1977). Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. I. Chemical composition. Annals of the rheumatic diseases, 36(2), 121–129. https://doi.org/10.1136/ard.36.2.121

[572] de Paz-Lugo, P., Lupiáñez, J. A., & Meléndez-Hevia, E. (2018). High glycine concentration increases collagen synthesis by articular chondrocytes in vitro: acute glycine deficiency could be an important cause of osteoarthritis. Amino acids, 50(10), 1357–1365. https://doi.org/10.1007/s00726-018-2611-x

[573] Kim, MH., Kim, HM. & Jeong, HJ. Estrogen-like osteoprotective effects of glycine in in vitro and in vivo models of menopause. Amino Acids 48, 791–800 (2016). https://doi.org/10.1007/s00726-015-2127-6

[574] Vieira, C. P., Viola, M., Carneiro, G. D., D'Angelo, M. L., Vicente, C. P., Passi, A., & Pimentel, E. R. (2018). Glycine improves the remodeling process of tenocytes in vitro. Cell biology international, 42(7), 804–814. https://doi.org/10.1002/cbin.10937

[575] Vieira, C. P., Guerra, F., de Oliveira, L. P., Almeida, M. S., Marcondes, M. C., & Pimentell, E. R. (2015). Green tea and glycine aid in the recovery of tendinitis of the Achilles tendon of rats.

Connective tissue research, 56(1), 50–58. https://doi.org/10.3109/03008207.2014.983270

[576] Kiers, J. L., & Bult, J. (2021). Mildly Processed Natural Eggshell Membrane Alleviates Joint Pain Associated with Osteoarthritis of the Knee: A Randomized Double-Blind Placebo-Controlled Study. Journal of medicinal food, 24(3), 292–298. https://doi.org/10.1089/jmf.2020.0034

[577] Hewlings, S., Kalman, D., & Schneider, L. V. (2019). A Randomized, Double-Blind, Placebo-Controlled, Prospective Clinical Trial Evaluating Water-Soluble Chicken Eggshell Membrane for Improvement in Joint Health in Adults with Knee Osteoarthritis. Journal of medicinal food, 22(9), 875–884. https://doi.org/10.1089/jmf.2019.0068

[578] Ruff, K. J., Winkler, A., Jackson, R. W., DeVore, D. P., & Ritz, B. W. (2009). Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study. Clinical rheumatology, 28(8), 907–914. https://doi.org/10.1007/s10067-009-1173-4

[579] Ruff, K. J., DeVore, D. P., Leu, M. D., & Robinson, M. A. (2009). Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. Clinical interventions in aging, 4, 235–240. https://doi.org/10.2147/cia.s5797

[580] Ruff, K. J., Morrison, D., Duncan, S. A., Back, M., Aydogan, C., & Theodosakis, J. (2018). Beneficial effects of natural eggshell membrane versus placebo in exercise-induced joint pain, stiffness, and cartilage turnover in healthy, postmenopausal women. Clinical interventions in aging, 13, 285–295. https://doi.org/10.2147/CIA.S153782

[581] Ketenci, A. (2019). Efficacy and Safety of Natural Eggshell Membrane (NEM®) in Patients with Grade 2/3 Knee Osteoarthritis: A Multi-Center, Randomized, Doubleblind, Placebo-Controlled, Single-crossover Clinical Study. Journal of The American Helicopter Society.

[582] Ruff, K. J., Kopp, K. J., Von Behrens, P., Lux, M., Mahn, M., & Back, M. (2016). Effectiveness of NEM® brand eggshell membrane in the treatment of suboptimal joint function in dogs: a multicenter, randomized, double-blind, placebo-controlled study. Veterinary medicine (Auckland, N.Z.), 7, 113–121. https://doi.org/10.2147/VMRR.S101842

[583] Cánovas, F., Abellán-Ruíz, M. S., García-Muñoz, A. M., Luque-Rubia, A. J., Victoria-Montesinos, D., Pérez-Piñero, S., Sánchez-Macarro, M., & López-Román, F. J. (2022). Randomised Clinical Trial to Analyse the Efficacy of Eggshell Membrane to Improve Joint Functionality in Knee Osteoarthritis. Nutrients, 14(11), 2340. https://doi.org/10.3390/nu14112340

[584] Benson, K. F., Ruff, K. J., & Jensen, G. S. (2012). Effects of natural eggshell membrane (NEM) on cytokine production in cultures of peripheral blood mononuclear cells: increased suppression of tumor necrosis factor-α levels after in vitro digestion. Journal of medicinal food, 15(4), 360–368. https://doi.org/10.1089/jmf.2011.0197

[585] Ruff, K. J., Durham, P. L., O'Reilly, A., & Long, F. D. (2015). Eggshell membrane hydrolyzates activate NF-κB in vitro: possible implications for in vivo efficacy. Journal of inflammation research, 8, 49–57. https://doi.org/10.2147/JIR.S78118

[586] Jia, H., Hanate, M., Aw, W., Itoh, H., Saito, K., Kobayashi, S., Hachimura, S., Fukuda, S., Tomita, M., Hasebe, Y., & Kato, H. (2017). Eggshell membrane powder ameliorates intestinal inflammation by facilitating the restitution of epithelial injury and alleviating microbial dysbiosis. Scientific reports, 7, 43993. https://doi.org/10.1038/srep43993

[587] Moreau, T., Gautron, J., Hincke, M. T., Monget, P., Réhault-Godbert, S., & Guyot, N. (2022). Antimicrobial Proteins and Peptides in Avian Eggshell: Structural Diversity and Potential Roles in Biomineralization. Frontiers in immunology, 13, 946428. https://doi.org/10.3389/fimmu.2022.946428

[588] Yoo, J., Park, K., Yoo, Y., Kim, J., Yang, H., & Shin, Y. (2014). Effects of Egg Shell Membrane Hydrolysates on Anti-Inflammatory, Anti-Wrinkle, Anti-Microbial Activity and Moisture-Protection. Korean journal for food science of animal resources, 34(1), 26–32. https://doi.org/10.5851/kosfa.2014.34.1.26

[589] Kalman, D. S., & Hewlings, S. (2020). The effect of oral hydrolyzed eggshell membrane on the appearance of hair, skin, and nails in healthy middle-aged adults: A randomized double-blind placebo-controlled clinical trial. Journal of cosmetic dermatology, 19(6), 1463–1472. https://doi.org/10.1111/jocd.13275

[590] Ohto-Fujita, E., Konno, T., Shimizu, M., Ishihara, K., Sugitate, T., Miyake, J., Yoshimura, K., Taniwaki, K., Sakurai, T., Hasebe, Y., & Atomi, Y. (2011). Hydrolyzed eggshell membrane immobilized on phosphorylcholine polymer supplies extracellular matrix environment for human dermal fibroblasts. Cell and tissue research, 345(1), 177–190. https://doi.org/10.1007/s00441-011-1172-z

[591] Vuong, T. T., Rønning, S. B., Ahmed, T., Brathagen, K., Høst, V., Hincke, M. T., Suso, H. P., & Pedersen, M. E. (2018). Processed eggshell membrane powder regulates cellular functions and increase MMP-activity important in early wound healing processes. PloS one, 13(8), e0201975. https://doi.org/10.1371/journal.pone.0201975

[592] Maheu, E., Rannou, F., & Reginster, J. Y. (2016). Efficacy and safety of hyaluronic acid in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Seminars in arthritis and rheumatism, 45(4 Suppl), S28–S33. https://doi.org/10.1016/j.semarthrit.2015.11.008

[593] Stecco, C., Stern, R., Porzionato, A., Macchi, V., Masiero, S., Stecco, A., & De Caro, R. (2011). Hyaluronan within fascia in the etiology of myofascial pain. Surgical and radiologic anatomy : SRA, 33(10), 891–896. https://doi.org/10.1007/s00276-011-0876-9

[594] Toole B. P. (2000). Hyaluronan is not just a goo!. The Journal of clinical investigation, 106(3), 335–336. https://doi.org/10.1172/JCI10706

[595] Fraser, J.R.E., Laurent, T.C. and Laurent, U.B.G. (1997), Hyaluronan: its nature, distribution, functions and turnover. Journal of Internal Medicine, 242: 27-33. https://doi.org/10.1046/j.1365-2796.1997.00170.x

[596] VAD (2019) 'Do Hyaluronic Acid Injections Work for Knee Osteoarthritis?', Accessed Online: https://www.arthritis-health.com/treatment/injections/do-hyaluronic-acid-injections-work-knee-osteoarthritis

[597] Altman, R. D., Manjoo, A., Fierlinger, A., Niazi, F., & Nicholls, M. (2015). The mechanism of action for hyaluronic acid treatment in the osteoarthritic knee: a systematic review. BMC musculoskeletal disorders, 16, 321. https://doi.org/10.1186/s12891-015-0775-z

[598] Phillips, M., Vannabouathong, C., Devji, T., Patel, R., Gomes, Z., Patel, A., Dixon, M., & Bhandari, M. (2020). Differentiating factors of intra-articular injectables have a meaningful impact on knee osteoarthritis outcomes: a network meta-analysis. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 28(9), 3031–3039. https://doi.org/10.1007/s00167-019-05763-1

[599] Tashiro, T., Seino, S., Sato, T., Matsuoka, R., Masuda, Y., & Fukui, N. (2012). Oral administration of polymer hyaluronic acid alleviates symptoms of knee osteoarthritis: a double-blind, placebo-controlled study over a 12-month period. TheScientificWorldJournal, 2012, 167928. https://doi.org/10.1100/2012/167928

[600] Shaharudin, A., & Aziz, Z. (2016). Effectiveness of hyaluronic acid and its derivatives on chronic wounds: a systematic review. Journal of wound care, 25(10), 585–592. https://doi.org/10.12968/jowc.2016.25.10.585

[601] Kawada, C., Yoshida, T., Yoshida, H., Matsuoka, R., Sakamoto, W., Odanaka, W., Sato, T., Yamasaki, T., Kanemitsu, T., Masuda, Y., & Urushibata, O. (2014). Ingested hyaluronan moisturizes dry skin. Nutrition journal, 13, 70. https://doi.org/10.1186/1475-2891-13-70

[602] Tammi, R., Ripellino, J. A., Margolis, R. U., Maibach, H. I., & Tammi, M. (1989). Hyaluronate accumulation in human epidermis treated with retinoic acid in skin organ culture. The Journal of investigative dermatology, 92(3), 326–332. https://doi.org/10.1111/1523-1747.ep12277125

[603] Averbeck, M., Gebhardt, C. A., Voigt, S., Beilharz, S., Anderegg, U., Termeer, C. C., Sleeman, J. P., & Simon, J. C. (2007). Differential Regulation of Hyaluronan Metabolism in the Epidermal and Dermal Compartments of Human Skin by UVB Irradiation. Journal of Investigative Dermatology, 127(3), 687–697. https://doi.org/10.1038/sj.jid.5700614

[604] Stern R. (2004). Hyaluronan catabolism: a new metabolic pathway. European journal of cell biology, 83(7), 317–325. https://doi.org/10.1078/0171-9335-00392

[605] Holmes, M. W., Bayliss, M. T., & Muir, H. (1988). Hyaluronic acid in human articular cartilage. Age-related changes in content and size. The Biochemical journal, 250(2), 435–441. https://doi.org/10.1042/bj2500435

[606] Shanthi M, Pekka P, Norrving B (2011). Global Atlas on Cardiovascular Disease Prevention and Control (PDF). World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. pp. 3–18. ISBN 978-92-4-156437-3.

[607] GBD 2015 Mortality and Causes of Death Collaborators (2016). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England), 388(10053), 1459–1544. https://doi.org/10.1016/S0140-6736(16)31012-1

[608] GBD 2013 Mortality and Causes of Death Collaborators (2015). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.

Lancet (London, England), 385(9963), 117–171. https://doi.org/10.1016/S0140-6736(14)61682-2

[609] American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2013). Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation, 127(1), e6–e245. https://doi.org/10.1161/CIR.0b013e31828124ad

[610] O'Donnell et al (2016). Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet (London, England), 388(10046), 761–775. https://doi.org/10.1016/S0140-6736(16)30506-2

[611] McGill, H. C., Jr, McMahan, C. A., & Gidding, S. S. (2008). Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. Circulation, 117(9), 1216–1227. https://doi.org/10.1161/CIRCULATIONAHA.107.717033

[612] Petersen, K. S., & Kris-Etherton, P. M. (2021). Diet Quality Assessment and the Relationship between Diet Quality and Cardiovascular Disease Risk. Nutrients, 13(12), 4305. https://doi.org/10.3390/nu13124305

[613] Salonen, J. T., Korpela, H., Salonen, R., Nyyssonen, K., Yla-Herttuala, S., Yamamoto, R., … Witztum, J. L. (1992). Autoantibody against oxidised LDL and progression of carotid atherosclerosis. The Lancet, 339(8798), 883–887. doi:10.1016/0140-6736(92)90926-t

[614] Holvoet, P., Stassen, J.-M., Van Cleemput, J., Collen, D., & Vanhaecke, J. (1998). Oxidized Low Density Lipoproteins in Patients With Transplant-Associated Coronary Artery Disease. Arteriosclerosis, Thrombosis, and Vascular Biology, 18(1), 100–107. doi:10.1161/01.atv.18.1.100

[615] Holvoet, P., Vanhaecke, J., Janssens, S., Van de Werf, F., & Collen, D. (1998). Oxidized LDL and Malondialdehyde-Modified LDL in Patients With Acute Coronary Syndromes and Stable Coronary

Artery Disease. Circulation, 98(15), 1487–1494. doi:10.1161/01.cir.98.15.1487

[616] Parthasarathy S et al (2012) 'Oxidized Low-Density Lipoprotein', Methods Mol Biol. 2010; 610: 403–417.

[617] DiNicolantonio, J. J., & Lucan, S. C. (2014). The wrong white crystals: not salt but sugar as aetiological in hypertension and cardiometabolic disease. Open heart, 1(1), e000167. https://doi.org/10.1136/openhrt-2014-000167

[618] DiNicolantonio, J. J., Lucan, S. C., & O'Keefe, J. H. (2016). The Evidence for Saturated Fat and for Sugar Related to Coronary Heart Disease. Progress in cardiovascular diseases, 58(5), 464–472. https://doi.org/10.1016/j.pcad.2015.11.006

[619] DiNicolantonio, J. J., Mehta, V., Onkaramurthy, N., & O'Keefe, J. H. (2018). Fructose-induced inflammation and increased cortisol: A new mechanism for how sugar induces visceral adiposity. Progress in cardiovascular diseases, 61(1), 3–9. https://doi.org/10.1016/j.pcad.2017.12.001

[620] DiNicolantonio, J. J., & OKeefe, J. H. (2017). Added sugars drive coronary heart disease via insulin resistance and hyperinsulinaemia: a new paradigm. Open heart, 4(2), e000729. https://doi.org/10.1136/openhrt-2017-000729

[621] DiNicolantonio, J. J., Subramonian, A. M., & O'Keefe, J. H. (2017). Added fructose as a principal driver of non-alcoholic fatty liver disease: a public health crisis. Open heart, 4(2), e000631. https://doi.org/10.1136/openhrt-2017-000631

[622] DiNicolantonio, J. J., & Berger, A. (2016). Added sugars drive nutrient and energy deficit in obesity: a new paradigm. Open heart, 3(2), e000469. https://doi.org/10.1136/openhrt-2016-000469

[623] DiNicolantonio, J. J., & O'Keefe, J. H. (2016). Hypertension Due to Toxic White Crystals in the Diet: Should We Blame Salt or Sugar?. Progress in cardiovascular diseases, 59(3), 219–225. https://doi.org/10.1016/j.pcad.2016.07.004

[624] DiNicolantonio, J. J., & Lucan, S. C. (2015). Is fructose malabsorption a cause of irritable bowel syndrome?. Medical hypotheses, 85(3), 295–297. https://doi.org/10.1016/j.mehy.2015.05.019

[625] DiNicolantonio, J. J., Mehta, V., Zaman, S. B., & O'Keefe, J. H. (2018). Not Salt But Sugar As Aetiological In Osteoporosis: A Review. Missouri medicine, 115(3), 247–252.

[626] DiNicolantonio J. J. (2016). Increase in the intake of refined carbohydrates and sugar may have led to the health decline of the Greenland Eskimos. Open heart, 3(2), e000444. https://doi.org/10.1136/openhrt-2016-000444

[627] DiNicolantonio, J. J., & O'Keefe, J. (2017). Markedly increased intake of refined carbohydrates and sugar is associated with the rise of coronary heart disease and diabetes among the Alaskan Inuit. Open heart, 4(2), e000673. https://doi.org/10.1136/openhrt-2017-000673

[628] Barnard N et al (2014) 'Saturated and trans fats and dementia: a systematic review', Neurobiology of Aging, Volume 35, Supplement 2, September 2014, Pages S65-S73.

[629] Pase CS et al (2013) 'Influence of perinatal trans fat on behavioral responses and brain oxidative status of adolescent rats acutely exposed to stress', Neuroscience. 2013 Sep 5;247:242-52.

[630] Di Pino and DeFronzo (2019) 'Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents', Endocrine Reviews, Volume 40, Issue 6, December 2019, Pages 1447–1467.

[631] Arnett et al (2000) 'Hypertension and arterial stiffness: The atherosclerosis risk in communities study', American Journal of Hypertension, Volume 13, Issue 4, April 2000, Pages 317–323.

[632] McNeill, A. M., Rosamond, W. D., Girman, C. J., Golden, S. H., Schmidt, M. I., East, H. E., Ballantyne, C. M., & Heiss, G. (2005). The metabolic syndrome and 11-year risk of incident cardiovascular

disease in the atherosclerosis risk in communities study. Diabetes care, 28(2), 385–390. https://doi.org/10.2337/diacare.28.2.385

[633] Jackson, C. L., Redline, S., & Emmons, K. M. (2015). Sleep as a potential fundamental contributor to disparities in cardiovascular health. Annual review of public health, 36, 417–440. https://doi.org/10.1146/annurev-publhealth-031914-122838

[634] NIH (2022) 'What Is Atherosclerosis?', Accessed Online November 16 2022: https://www.nhlbi.nih.gov/health/atherosclerosis

[635] Aronow WS, Fleg JL, Rich MW (2013). Tresch and Aronow's Cardiovascular Disease in the Elderly, Fifth Edition. CRC Press. p. 171.

[636] Shor A (2008). Chlamydia Atherosclerosis Lesion: Discovery, Diagnosis and Treatment. Springer Science & Business Media. p. 8.

[637] Aviram, M., & Fuhrman, B. (1998). LDL oxidation by arterial wall macrophages depends on the oxidative status in the lipoprotein and in the cells: role of prooxidants vs. antioxidants. Molecular and cellular biochemistry, 188(1-2), 149–159.

[638] NIH (2022) 'Causes and Risk Factors', Atherosclerosis, Accessed Online Nov 16 2022: https://www.nhlbi.nih.gov/health/atherosclerosis/causes

[639] Lind L. (2003). Circulating markers of inflammation and atherosclerosis. Atherosclerosis, 169(2), 203–214. https://doi.org/10.1016/s0021-9150(03)00012-1

[640] Wong, A.P., A.L. Mohamed, and A. Niedzwieck, Atherosclerosis and the Cholesterol Theory: A Reappraisal. World Journal of Cardiovascular Diseases, 2016. 6: p. 391-409.

[641] Wong, A.P., A.L. Mohamed, and A. Niedzwieck, Atherosclerosis and the Cholesterol Theory: A Reappraisal. World Journal of Cardiovascular Diseases, 2016. 6: p. 391-409.

[642] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can

Med Assoc J, 1941. 44(2): p. 114-20.

[643] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can Med Assoc J, 1941. 44(2): p. 114-20.

[644] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can Med Assoc J, 1941. 44(2): p. 114-20.

[645] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can Med Assoc J, 1941. 44(2): p. 114-20.

[646] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can Med Assoc J, 1941. 44(2): p. 114-20.

[647] Paterson, J.C., Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi. Can Med Assoc J, 1941. 44(2): p. 114-20.

[648] Pemberton (2006) 'Medical experiments carried out in Sheffield on conscientious objectors to military service during the 1939–45 war', International Journal of Epidemiology, Volume 35, Issue 3, June 2006, Pages 556–558.

[649] May, J. M., & Harrison, F. E. (2013). Role of vitamin C in the function of the vascular endothelium. Antioxidants & redox signaling, 19(17), 2068–2083. https://doi.org/10.1089/ars.2013.5205

[650] Juraschek, S. P., Guallar, E., Appel, L. J., & Miller, E. R., 3rd (2012). Effects of vitamin C supplementation on blood pressure: a meta-analysis of randomized controlled trials. The American journal of clinical nutrition, 95(5), 1079–1088. https://doi.org/10.3945/ajcn.111.027995

[651] May, J. M., & Harrison, F. E. (2013). Role of vitamin C in the function of the vascular endothelium. Antioxidants & redox signaling, 19(17), 2068–2083. https://doi.org/10.1089/ars.2013.5205

[652] WILLIS, G. C., LIGHT, A. W., & GOW, W. S. (1954). Serial arteriography in atherosclerosis. Canadian Medical Association journal, 71(6), 562–568.

[653] Deruelle, F., & Baron, B. (2008). Vitamin C: is supplementation necessary for optimal health?. Journal of alternative and complementary medicine (New York, N.Y.), 14(10), 1291–1298. https://doi.org/10.1089/acm.2008.0165

[654] Ordman, A.R., Vitamin C twice a day enhances health. Health, 2010. 2(8): p. 819-823.

[655] Hickey, S., & Roberts, H. (2005). Misleading information on the properties of vitamin C. PLoS medicine, 2(9), e307–e309. https://doi.org/10.1371/journal.pmed.0020307

[656] Steve Hickey, Gert Schuitemaker, Atsuo Yanagisawa, Leonardo Noriega, Michael J. González, Jorge R. Miranda-Massari, Caroline Chibelushi & Damien Downing (2015) Archaic RDA Methodology for Vitamin C, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2012.747486

[657] Institute of Medcine (2000) 'Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids', Washington, DC: National Academy Press, 2000.

[658] Ordman, A. R. (2010). Vitamin C twice a day enhances health. Health, 02(08), 819–823. doi:10.4236/health.2010.28123

[659] Carr and Frei (1999) 'Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans', The American Journal of Clinical Nutrition, Volume 69, Issue 6, June 1999, Pages 1086–1107.

[660] Frei et al (2012) Authors' Perspective: What is the Optimum Intake of Vitamin C in Humans?, Critical Reviews in Food Science and Nutrition, 52:9, 815-829.

[661] Ordman (2010) 'Vitamin C twice a day enhances health', Health 2(08):819-823.

[662] Willcox, B. J., Curb, J. D., & Rodriguez, B. L. (2008). Antioxidants in cardiovascular health and disease: key lessons from epidemiologic studies. The American journal of cardiology, 101(10A), 75D–86D. https://doi.org/10.1016/j.amjcard.2008.02.012

[663] Ye, Z., & Song, H. (2008). Antioxidant vitamins intake and the risk of coronary heart disease: meta-analysis of cohort studies. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 15(1), 26–34. https://doi.org/10.1097/HJR.0b013e3282f11f95

[664] NIH (2021) 'Vitamin C', Fact Sheet for Health Professionals: Accessed Online November 16th 2022: https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/

[665] Harris, E. D., & Percival, S. S. (1991). A role for ascorbic acid in copper transport. The American journal of clinical nutrition, 54(6 Suppl), 1193S–1197S. https://doi.org/10.1093/ajcn/54.6.1193s

[666] Milne, D. B., & Omaye, S. T. (1980). Effect of vitamin C on copper and iron metabolism in the guinea pig. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition, 50(3), 301–308.

[667] Boyera, N., Galey, I., & Bernard, B. A. (1998). Effect of vitamin C and its derivatives on collagen synthesis and cross-linking by normal human fibroblasts. International journal of cosmetic science, 20(3), 151–158. https://doi.org/10.1046/j.1467-2494.1998.171747.x

[668] Barsony, J., Sugimura, Y., & Verbalis, J. G. (2011). Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. The Journal of biological chemistry, 286(12), 10864–10875. https://doi.org/10.1074/jbc.M110.155002

[669] Ruiz-Ramírez, A., Ortiz-Balderas, E., Cardozo-Saldaña, G., Diaz-Diaz, E., & El-Hafidi, M. (2014). Glycine restores glutathione and protects against oxidative stress in vascular tissue from sucrose-fed rats. Clinical science (London, England : 1979), 126(1), 19–29. https://doi.org/10.1042/CS20130164

[670] Sekhar, R. V., Liu, C. W., & Rice, S. (2015). Increasing glutathione concentrations with cysteine and glycine supplementation lowers inflammation in HIV patients. AIDS (London, England), 29(14), 1899–1900. https://doi.org/10.1097/QAD.0000000000000792

[671] Dinescu, A., Brown, T. R., Barelier, S., Cundari, T. R., & Anderson, M. E. (2010). The role of the glycine triad in human glutathione synthetase. Biochemical and biophysical research communications, 400(4), 511–516. https://doi.org/10.1016/j.bbrc.2010.08.081

[672] McCarty et al (2019) 'Activated Glycine Receptors May Decrease Endosomal NADPH Oxidase Activity by Opposing ClC-3-Mediated Efflux of Chloride from Endosomes', Medical Hypotheses 123, DOI: 10.1016/j.mehy.2019.01.012

[673] Cieslik, K. A., Sekhar, R. V., Granillo, A., Reddy, A., Medrano, G., Heredia, C. P., Entman, M. L., Hamilton, D. J., Li, S., Reineke, E., Gupte, A. A., Zhang, A., & Taffet, G. E. (2018). Improved Cardiovascular Function in Old Mice After N-Acetyl Cysteine and Glycine Supplemented Diet: Inflammation and Mitochondrial Factors. The journals of gerontology. Series A, Biological sciences and medical sciences, 73(9), 1167–1177. https://doi.org/10.1093/gerona/gly034

[674] Ding, Y., Svingen, G. F., Pedersen, E. R., Gregory, J. F., Ueland, P. M., Tell, G. S., & Nygård, O. K. (2015). Plasma Glycine and Risk of Acute Myocardial Infarction in Patients With Suspected Stable Angina Pectoris. Journal of the American Heart Association, 5(1), e002621. https://doi.org/10.1161/JAHA.115.002621

[675] Hasegawa, S., Ichiyama, T., Sonaka, I., Ohsaki, A., Okada, S., Wakiguchi, H., Kudo, K., Kittaka, S., Hara, M., & Furukawa, S. (2012). Cysteine, histidine and glycine exhibit anti-inflammatory effects in human coronary arterial endothelial cells. Clinical and experimental immunology, 167(2), 269–274. https://doi.org/10.1111/j.1365-2249.2011.04519.x

[676] Guo, D., Murdoch, C. E., Xu, H., Shi, H., Duan, D. D., Ahmed, A., & Gu, Y. (2017). Vascular endothelial growth factor signaling requires glycine to promote angiogenesis. Scientific reports, 7(1), 14749. https://doi.org/10.1038/s41598-017-15246-3

[677] Sim, W. C., Han, I., Lee, W., Choi, Y. J., Lee, K. Y., Kim, D. G., Jung, S. H., Oh, S. H., & Lee, B. H. (2016). Inhibition of homocysteine-induced endoplasmic reticulum stress and endothelial cell damage by l-serine and glycine. Toxicology in vitro : an international journal published in association with BIBRA, 34, 138–145. https://doi.org/10.1016/j.tiv.2016.04.004

[678] Venkatesh, R., Srinivasan, K., & Singh, S. A. (2017). Effect of arginine:lysine and glycine:methionine intake ratios on dyslipidemia and selected biomarkers implicated in cardiovascular disease: A study with hypercholesterolemic rats. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 91, 408–414. https://doi.org/10.1016/j.biopha.2017.04.072

[679] Zeb, A., & Rahman, S. U. (2017). Protective effects of dietary glycine and glutamic acid toward the toxic effects of oxidized mustard oil in rabbits. Food & function, 8(1), 429–436. https://doi.org/10.1039/c6fo01329e

[680] Elsey, D. J., Fowkes, R. C., & Baxter, G. F. (2010). L-cysteine stimulates hydrogen sulfide synthesis in myocardium associated with attenuation of ischemia-reperfusion injury. Journal of cardiovascular pharmacology and therapeutics, 15(1), 53–59. https://doi.org/10.1177/1074248409357743

[681] Kusche, W., Paxinos, R., Haselmann, J., Schwantes, U., & Breddin, H. K. (2003). Acetylsalicylic acid tablets with glycine

improve long-term tolerability in antiplatelet drug therapy: results of a noninterventional trial. Advances in therapy, 20(5), 237–245. https://doi.org/10.1007/BF02849852

[682] Zhang, Y., Lv, S. J., Yan, H., Wang, L., Liang, G. P., Wan, Q. X., & Peng, X. (2013). Effects of glycine supplementation on myocardial damage and cardiac function after severe burn. Burns : journal of the International Society for Burn Injuries, 39(4), 729–735. https://doi.org/10.1016/j.burns.2012.09.006

[683] Schemmer, P., Zhong, Z., Galli, U., Wheeler, M. D., Xiangli, L., Bradford, B. U., Conzelmann, L. O., Forman, D., Boyer, J., & Thurman, R. G. (2013). Glycine reduces platelet aggregation. Amino acids, 44(3), 925–931. https://doi.org/10.1007/s00726-012-1422-8

[684] Wang, W., Wu, Z., Dai, Z., Yang, Y., Wang, J., & Wu, G. (2013). Glycine metabolism in animals and humans: implications for nutrition and health. Amino acids, 45(3), 463–477. https://doi.org/10.1007/s00726-013-1493-1

[685] Mayo Clinic (2021) 'Myocardial ischemia', Accessed Online November 19th 2022: https://www.mayoclinic.org/diseases-conditions/myocardial-ischemia/symptoms-causes/syc-20375417

[686] World Health Organization Department of Health Statistics and Informatics in the Information, Evidence and Research Cluster (2004). The global burden of disease 2004 update. Geneva: WHO.

[687] Medline (2018) 'Ischemic Stroke', Accessed Online November 20 2022: https://medlineplus.gov/ischemicstroke.html

[688] Garcia-Santos, D., Schranzhofer, M., Bergeron, R., Sheftel, A. D., & Ponka, P. (2017). Extracellular glycine is necessary for optimal hemoglobinization of erythroid cells. Haematologica, 102(8), 1314–1323. https://doi.org/10.3324/haematol.2016.155671

[689] Yao, W., Ji, F., Chen, Z., Zhang, N., Ren, S. Q., Zhang, X. Y., Liu, S. Y., & Lu, W. (2012). Glycine exerts dual roles in ischemic injury through distinct mechanisms. Stroke, 43(8), 2212–2220. https://doi.org/10.1161/STROKEAHA.111.645994

[690] Sommer, S. P., Sommer, S., Sinha, B., & Leyh, R. G. (2012). Glycine preconditioning to ameliorate pulmonary ischemia reperfusion injury in rats. Interactive cardiovascular and thoracic surgery, 14(5), 521–525. https://doi.org/10.1093/icvts/ivs008

[691] Sheth, H., Hafez, T., Glantzounis, G. K., Seifalian, A. M., Fuller, B., & Davidson, B. R. (2011). Glycine maintains mitochondrial activity and bile composition following warm liver ischemia-reperfusion injury. Journal of gastroenterology and hepatology, 26(1), 194–200. https://doi.org/10.1111/j.1440-1746.2010.06323.x

[692] Zhang, Y., Su, W., Zhang, Q., Xu, J., Liu, H., Luo, J., Zhan, L., Xia, Z., & Lei, S. (2018). Glycine Protects H9C2 Cardiomyocytes from High Glucose- and Hypoxia/Reoxygenation-Induced Injury via Inhibiting PKCβ2 Activation and Improving Mitochondrial Quality. Journal of diabetes research, 2018, 9502895. https://doi.org/10.1155/2018/9502895

[693] Al-Saeedi, M., Nickkholgh, A., Schultze, D., Flechtenmacher, C., Zorn, M., Liang, R., Gutt, C. N., & Schemmer, P. (2018). Glycine Protects the Liver from Reperfusion Injury following Pneumoperitoneum. European surgical research. Europaische chirurgische Forschung. Recherches chirurgicales europeennes, 59(1-2), 91–99. https://doi.org/10.1159/000490309

[694] Bruns, H., Watanpour, I., Gebhard, M. M., Flechtenmacher, C., Galli, U., Schulze-Bergkamen, H., Zorn, M., Büchler, M. W., & Schemmer, P. (2011). Glycine and taurine equally prevent fatty livers from Kupffer cell-dependent injury: an in vivo microscopy study. Microcirculation (New York, N.Y. : 1994), 18(3), 205–213. https://doi.org/10.1111/j.1549-8719.2010.00078.x

[695] Lutchmansingh, F. K., Hsu, J. W., Bennett, F. I., Badaloo, A. V., McFarlane-Anderson, N., Gordon-Strachan, G. M., Wright-Pascoe, R. A., Jahoor, F., & Boyne, M. S. (2018). Glutathione metabolism in type 2 diabetes and its relationship with microvascular complications and glycemia. PloS one, 13(6), e0198626. https://doi.org/10.1371/journal.pone.0198626

[696] Sekhar, R. V., McKay, S. V., Patel, S. G., Guthikonda, A. P., Reddy, V. T., Balasubramanyam, A., & Jahoor, F. (2011). Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diabetes care, 34(1), 162–167. https://doi.org/10.2337/dc10-1006

[697] Adeva-Andany, M., Souto-Adeva, G., Ameneiros-Rodríguez, E., Fernández-Fernández, C., Donapetry-García, C., & Domínguez-Montero, A. (2018). Insulin resistance and glycine metabolism in humans. Amino acids, 50(1), 11–27. https://doi.org/10.1007/s00726-017-2508-0

[698] Liao, Y. J., Lee, T. S., Twu, Y. C., Hsu, S. M., Yang, C. P., Wang, C. K., Liang, Y. C., & Chen, Y. A. (2016). Glycine N-methyltransferase deficiency in female mice impairs insulin signaling and promotes gluconeogenesis by modulating the PI3K/Akt pathway in the liver. Journal of biomedical science, 23(1), 69. https://doi.org/10.1186/s12929-016-0278-8

[699] Yan-Do, R., Duong, E., Manning Fox, J. E., Dai, X., Suzuki, K., Khan, S., Bautista, A., Ferdaoussi, M., Lyon, J., Wu, X., Cheley, S., MacDonald, P. E., & Braun, M. (2016). A Glycine-Insulin Autocrine Feedback Loop Enhances Insulin Secretion From Human β-Cells and Is Impaired in Type 2 Diabetes. Diabetes, 65(8), 2311–2321. https://doi.org/10.2337/db15-1272

[700] Yan-Do, R., & MacDonald, P. E. (2017). Impaired "Glycine"-mia in Type 2 Diabetes and Potential Mechanisms Contributing to Glucose Homeostasis. Endocrinology, 158(5), 1064–1073. https://doi.org/10.1210/en.2017-00148

[701] El-Hafidi, M., Franco, M., Ramírez, A. R., Sosa, J. S., Flores, J. A. P., Acosta, O. L., Salgado, M. C., & Cardoso-Saldaña, G. (2018). Glycine Increases Insulin Sensitivity and Glutathione Biosynthesis and Protects against Oxidative Stress in a Model of Sucrose-Induced Insulin Resistance. Oxidative medicine and cellular longevity, 2018, 2101562. https://doi.org/10.1155/2018/2101562

[702] Nguyen, D., Hsu, J. W., Jahoor, F., & Sekhar, R. V. (2014). Effect of increasing glutathione with cysteine and glycine supplementation on mitochondrial fuel oxidation, insulin sensitivity, and body composition in older HIV-infected patients. The Journal of clinical endocrinology and metabolism, 99(1), 169–177. https://doi.org/10.1210/jc.2013-2376

[703] Lustgarten, M. S., Price, L. L., Phillips, E. M., & Fielding, R. A. (2013). Serum glycine is associated with regional body fat and insulin resistance in functionally-limited older adults. PloS one, 8(12), e84034. https://doi.org/10.1371/journal.pone.0084034

[704] Rochlani, Y., Pothineni, N. V., Kovelamudi, S., & Mehta, J. L. (2017). Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Therapeutic Advances in Cardiovascular Disease, 11(8), 215–225. doi:10.1177/1753944717711379

[705] Grundy, S. M., Hansen, B., Smith, S. C., Cleeman, J. I., & Kahn, R. A. (2004). Clinical Management of Metabolic Syndrome. Arteriosclerosis, Thrombosis, and Vascular Biology, 24(2). doi:10.1161/01.atv.0000112379.88385.67

[706] Mottillo, S., Filion, K. B., Genest, J., Joseph, L., Pilote, L., Poirier, P., … Eisenberg, M. J. (2010). The Metabolic Syndrome and Cardiovascular Risk. Journal of the American College of Cardiology, 56(14), 1113–1132. doi:10.1016/j.jacc.2010.05.034

[707] Moore, J. X., Chaudhary, N., & Akinyemiju, T. (2017). Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. Preventing Chronic Disease, 14. doi:10.5888/pcd14.160287

[708] Li et al (2018). Association of serum glycine levels with metabolic syndrome in an elderly Chinese population. Nutrition & Metabolism, 15(1). https://doi.org/10.1186/s12986-018-0325-4

[709] López, Y. R., Pérez-Torres, I., Zúñiga-Muñoz, A., Lans, V. G., Díaz-Díaz, E., Castro, E. S., & Espejel, R. V. (2016). Effect of Glycine on Adipocyte Hypertrophy in a Metabolic Syndrome Rat Model. Current drug delivery, 13(1), 158–169. https://doi.org/10.2174/1567201813011603141515 54

[710] Yue, J. T., Mighiu, P. I., Naples, M., Adeli, K., & Lam, T. K. (2012). Glycine normalizes hepatic triglyceride-rich VLDL secretion by triggering the CNS in high-fat fed rats. Circulation research, 110(10), 1345–1354. https://doi.org/10.1161/CIRCRESAHA.112.268276

[711] Imenshahidi, M., Hossenzadeh, H. Effects of glycine on metabolic syndrome components: a review. J Endocrinol Invest 45, 927–939 (2022). https://doi.org/10.1007/s40618-021-01720-3

[712] Chen, J., Ma, X., Yang, Y., Dai, Z., Wu, Z., & Wu, G. (2018). Glycine enhances expression of adiponectin and IL-10 in 3T3-L1 adipocytes without affecting adipogenesis and lipolysis. Amino acids, 50(5), 629–640. https://doi.org/10.1007/s00726-018-2537-3

[713] Pérez-Torres, I., Ibarra, B., Soria-Castro, E., Torrico-Lavayen, R., Pavón, N., Diaz-Diaz, E., Flores, P. L., Infante, O., & Baños, G. (2011). Effect of glycine on the cyclooxygenase pathway of the kidney arachidonic acid metabolism in a rat model of metabolic syndrome. Canadian journal of physiology and pharmacology, 89(12), 899–910. https://doi.org/10.1139/y11-086

[714] Ntzouvani, A., Nomikos, T., Panagiotakos, D., Fragopoulou, E., Pitsavos, C., McCann, A., Ueland, P. M., & Antonopoulou, S. (2017). Amino acid profile and metabolic syndrome in a male Mediterranean population: A cross-sectional study. Nutrition, metabolism, and cardiovascular diseases : NMCD, 27(11), 1021–1030. https://doi.org/10.1016/j.numecd.2017.07.006

[715] Price et al (August 2006). "Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death". Am. J. Clin. Nutr. 84 (2): 449–60.

[716] Laforest, S., Labrecque, J., Michaud, A., Cianflone, K., & Tchernof, A. (2015). Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. Critical Reviews in Clinical Laboratory Sciences, 52(6), 301–313. doi:10.3109/10408363.2015.1041582

[717] Bergman, R. N., Kim, S. P., Catalano, K. J., Hsu, I. R., Chiu, J. D., Kabir, M. , Hucking, K. and Ader, M. (2006), Why Visceral Fat is Bad: Mechanisms of the Metabolic Syndrome. Obesity, 14: 16S-19S.

[718] Matsuzawa, Y., Funahashi, T., & Nakamura, T. (2011). The Concept of Metabolic Syndrome: Contribution of Visceral Fat Accumulation and Its Molecular Mechanism. Journal of Atherosclerosis and Thrombosis, 18(8), 629–639. doi:10.5551/jat.7922

[719] Schröder, H., Morales-Molina, J. A., Bermejo, S., Barral, D., Mándoli, E. S., Grau, M., Guxens, M., de Jaime Gil, E., Alvarez, M. D., & Marrugat, J. (2007). Relationship of abdominal obesity with alcohol consumption at population scale. European journal of nutrition, 46(7), 369–376. https://doi.org/10.1007/s00394-007-0674-7

[720] Bendsen, N. T., Christensen, R., Bartels, E. M., Kok, F. J., Sierksma, A., Raben, A., & Astrup, A. (2013). Is beer consumption related to measures of abdominal and general obesity? A systematic review and meta-analysis. Nutrition reviews, 71(2), 67–87. https://doi.org/10.1111/j.1753-4887.2012.00548.x

[721] Elliott, S. S., Keim, N. L., Stern, J. S., Teff, K., & Havel, P. J. (2002). Fructose, weight gain, and the insulin resistance syndrome. The American journal of clinical nutrition, 76(5), 911–922. https://doi.org/10.1093/ajcn/76.5.911

[722] Stanhope, K. L., & Havel, P. J. (2010). Fructose consumption: recent results and their potential implications. Annals of the New York Academy of Sciences, 1190, 15–24. https://doi.org/10.1111/j.1749-6632.2009.05266.x

[723] Chen, C. Y., Wang, B. T., Wu, Z. C., Yu, W. T., Lin, P. J., Tsai, W. L., & Shiesh, S. C. (2013). Glycine ameliorates liver injury and vitamin D deficiency induced by bile duct ligation. Clinica chimica acta; international journal of clinical chemistry, 420, 150–154. https://doi.org/10.1016/j.cca.2012.10.016

[724] Pal, P. B., Pal, S., Das, J., & Sil, P. C. (2012). Modulation of mercury-induced mitochondria-dependent apoptosis by glycine in hepatocytes. Amino acids, 42(5), 1669–1683. https://doi.org/10.1007/s00726-011-0869-3

[725] Wang, Y. S., Yan, Y. H., & Zou, X. F. (2010). Protective effect of glycine on liver injury during liver transplantation. Chinese medical journal, 123(14), 1931–1938.

[726] Barakat, H. A., & Hamza, A. H. (2012). Glycine alleviates liver injury induced by deficiency in methionine and or choline in rats. European review for medical and pharmacological sciences, 16(6), 728–736.

[727] Blancas-Flores, G., Alarcón-Aguilar, F. J., García-Macedo, R., Almanza-Pérez, J. C., Flores-Sáenz, J. L., Román-Ramos, R., Ventura-Gallegos, J. L., Kumate, J., Zentella-Dehesa, A., & Cruz, M. (2012). Glycine suppresses TNF-α-induced activation of NF-κB in differentiated 3T3-L1 adipocytes. European journal of pharmacology, 689(1-3), 270–277. https://doi.org/10.1016/j.ejphar.2012.06.025

[728] Bhattacharyya, S., Ghosh, J., & Sil, P. C. (2012). Iron induces hepatocytes death via MAPK activation and mitochondria-dependent apoptotic pathway: beneficial role of glycine. Free radical research, 46(10), 1296–1307. https://doi.org/10.3109/10715762.2012.712690

[729] Zhou, X., Han, D., Xu, R., Wu, H., Qu, C., Wang, F., Wang, X., & Zhao, Y. (2016). Glycine protects against high sucrose and high fat-induced non-alcoholic steatohepatitis in rats. Oncotarget, 7(49), 80223–80237. https://doi.org/10.18632/oncotarget.12831

[730] McCarty, M. F., & DiNicolantonio, J. J. (2014). The cardiometabolic benefits of glycine: Is glycine an 'antidote' to dietary

fructose?. Open heart, 1(1), e000103. https://doi.org/10.1136/openhrt-2014-000103

[731] Koizumi, S., Inoue, N., Sugihara, F., & Igase, M. (2019). Effects of Collagen Hydrolysates on Human Brain Structure and Cognitive Function: A Pilot Clinical Study. Nutrients, 12(1), 50. https://doi.org/10.3390/nu12010050

[732] Huang, K. F., Hsu, W. C., Hsiao, J. K., Chen, G. S., & Wang, J. Y. (2014). Collagen-glycosaminoglycan matrix implantation promotes angiogenesis following surgical brain trauma. BioMed research international, 2014, 672409. https://doi.org/10.1155/2014/672409

[733] Chen, J. H., Hsu, W. C., Huang, K. F., & Hung, C. H. (2019). Neuroprotective Effects of Collagen-Glycosaminoglycan Matrix Implantation following Surgical Brain Injury. Mediators of inflammation, 2019, 6848943. https://doi.org/10.1155/2019/6848943

[734] Pei et al (2010) 'Marine collagen peptide isolated from Chum Salmon (Oncorhynchus keta) skin facilitates learning and memory in aged C57BL/6J mice', Food Chemistry, Volume 118, Issue 2, 15 January 2010, Pages 333-340.

[735] Gladstone Institutes. (2008, December 10). Collagen May Help Protect Brain Against Alzheimer's Disease. ScienceDaily. Retrieved November 20, 2022 from www.sciencedaily.com/releases/2008/12/081210150713.htm

[736] Tam, R. Y., Fuehrmann, T., Mitrousis, N., & Shoichet, M. S. (2014). Regenerative therapies for central nervous system diseases: a biomaterials approach. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 39(1), 169–188. https://doi.org/10.1038/npp.2013.237

[737] Friess W. (1998). Collagen--biomaterial for drug delivery. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 45(2), 113–136. https://doi.org/10.1016/s0939-6411(98)00017-4

[738] Miyata, T., Taira, T., & Noishiki, Y. (1992). Collagen engineering for biomaterial use. Clinical materials, 9(3-4), 139–148. https://doi.org/10.1016/0267-6605(92)90093-9

[739] Garbayo, E., Montero-Menei, C. N., Ansorena, E., Lanciego, J. L., Aymerich, M. S., & Blanco-Prieto, M. J. (2009). Effective GDNF brain delivery using microspheres--a promising strategy for Parkinson's disease. Journal of controlled release : official journal of the Controlled Release Society, 135(2), 119–126. https://doi.org/10.1016/j.jconrel.2008.12.010

[740] Dang, J. M., & Leong, K. W. (2006). Natural polymers for gene delivery and tissue engineering. Advanced drug delivery reviews, 58(4), 487–499. https://doi.org/10.1016/j.addr.2006.03.001

[741] Heya, T., Mikura, Y., Nagai, A., Miura, Y., Futo, T., Tomida, Y., Shimizu, H., & Toguchi, H. (1994). Controlled release of thyrotropin releasing hormone from microspheres: evaluation of release profiles and pharmacokinetics after subcutaneous administration. Journal of pharmaceutical sciences, 83(6), 798–801. https://doi.org/10.1002/jps.2600830608

[742] Zhong, Y., & Bellamkonda, R. V. (2008). Biomaterials for the central nervous system. Journal of the Royal Society, Interface, 5(26), 957–975. https://doi.org/10.1098/rsif.2008.0071

[743] Heino J. (2007). The collagen family members as cell adhesion proteins. BioEssays : news and reviews in molecular, cellular and developmental biology, 29(10), 1001–1010. https://doi.org/10.1002/bies.20636

[744] Kalluri, R. Basement membranes: structure, assembly and role in tumour angiogenesis. Nat Rev Cancer 3, 422–433 (2003). https://doi.org/10.1038/nrc1094

[745] Brown, W. R., & Thore, C. R. (2011). Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathology and applied neurobiology, 37(1), 56–74. https://doi.org/10.1111/j.1365-2990.2010.01139.x

[746] Khaing ZZ, Thomas RC, Geissler SA, Schmidt CE. Advanced biomaterials for repairing the nervous system: what can hydrogels do for the brain. Mater Today. 2014;17:332–340.
[747] Hoare, T. R., & Kohane, D. S. (2008). Hydrogels in drug delivery: Progress and challenges. Polymer, 49(8), 1993–2007. https://doi.org/10.1016/j.polymer.2008.01.027
[748] Lee, C. H., Singla, A., & Lee, Y. (2001). Biomedical applications of collagen. International journal of pharmaceutics, 221(1-2), 1–22. https://doi.org/10.1016/s0378-5173(01)00691-3
[749] Friess W. (1998). Collagen--biomaterial for drug delivery. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, 45(2), 113–136. https://doi.org/10.1016/s0939-6411(98)00017-4
[750] Foidl, B. M., Ucar, B., Schwarz, A., Rebelo, A. L., Pandit, A., & Humpel, C. (2018). Nerve growth factor released from collagen scaffolds protects axotomized cholinergic neurons of the basal nucleus of Meynert in organotypic brain slices. Journal of neuroscience methods, 295, 77–86. https://doi.org/10.1016/j.jneumeth.2017.12.003
[751] Nagai, N., Kumasaka, N., Kawashima, T., Kaji, H., Nishizawa, M., & Abe, T. (2010). Preparation and characterization of collagen microspheres for sustained release of VEGF. Journal of materials science. Materials in medicine, 21(6), 1891–1898. https://doi.org/10.1007/s10856-010-4054-0
[752] Kraskiewicz, H., Breen, B., Sargeant, T., McMahon, S., & Pandit, A. (2013). Assembly of protein-based hollow spheres encapsulating a therapeutic factor. ACS chemical neuroscience, 4(9), 1297–1304. https://doi.org/10.1021/cn400080h
[753] Popovic, N., & Brundin, P. (2006). Therapeutic potential of controlled drug delivery systems in neurodegenerative diseases. International journal of pharmaceutics, 314(2), 120–126. https://doi.org/10.1016/j.ijpharm.2005.09.040

[754] Khaing ZZ, Thomas RC, Geissler SA, Schmidt CE. Advanced biomaterials for repairing the nervous system: what can hydrogels do for the brain. Mater Today. 2014;17:332–340.

[755] Taras, J. S., Jacoby, S. M., & Lincoski, C. J. (2011). Reconstruction of digital nerves with collagen conduits. The Journal of hand surgery, 36(9), 1441–1446. https://doi.org/10.1016/j.jhsa.2011.06.009

[756] Jain, A., Kim, Y. T., McKeon, R. J., & Bellamkonda, R. V. (2006). In situ gelling hydrogels for conformal repair of spinal cord defects, and local delivery of BDNF after spinal cord injury. Biomaterials, 27(3), 497–504. https://doi.org/10.1016/j.biomaterials.2005.07.008

[757] Pakulska, M. M., Ballios, B. G., & Shoichet, M. S. (2012). Injectable hydrogels for central nervous system therapy. Biomedical materials (Bristol, England), 7(2), 024101. https://doi.org/10.1088/1748-6041/7/2/024101

[758] Joosten, E. A., Bär, P. R., & Gispen, W. H. (1995). Collagen implants and cortico-spinal axonal growth after mid-thoracic spinal cord lesion in the adult rat. Journal of neuroscience research, 41(4), 481–490. https://doi.org/10.1002/jnr.490410407

[759] Harris, K., Armstrong, S. P., Campos-Pires, R., Kiru, L., Franks, N. P., & Dickinson, R. (2013). Neuroprotection against traumatic brain injury by xenon, but not argon, is mediated by inhibition at the N-methyl-D-aspartate receptor glycine site. Anesthesiology, 119(5), 1137–1148. https://doi.org/10.1097/ALN.0b013e3182a2a265

[760] Tanabe, M., Nitta, A., & Ono, H. (2010). Neuroprotection via strychnine-sensitive glycine receptors during post-ischemic recovery of excitatory synaptic transmission in the hippocampus. Journal of pharmacological sciences, 113(4), 378–386. https://doi.org/10.1254/jphs.10150fp

[761] Chen, J., Zhuang, Y., Zhang, Z. F., Wang, S., Jin, P., He, C., Hu, P. C., Wang, Z. F., Li, Z. Q., Xia, G. M., Li, G., Wang, Y., & Wan,

Q. (2016). Glycine confers neuroprotection through microRNA-301a/PTEN signaling. Molecular brain, 9(1), 59. https://doi.org/10.1186/s13041-016-0241-3

[762] Chen, J., Hu, R., Liao, H., Zhang, Y., Lei, R., Zhang, Z., Zhuang, Y., Wan, Y., Jin, P., Feng, H., & Wan, Q. (2017). A non-ionotropic activity of NMDA receptors contributes to glycine-induced neuroprotection in cerebral ischemia-reperfusion injury. Scientific reports, 7(1), 3575. https://doi.org/10.1038/s41598-017-03909-0

[763] Bekri, A., & Drapeau, P. (2018). Glycine Promotes the Survival of a Subpopulation of Neural Stem Cells. Frontiers in cell and developmental biology, 6, 68. https://doi.org/10.3389/fcell.2018.00068

[764] Selin, A. A., Lobysheva, N. V., Vorontsova, O. N., Tonshin, A. A., Yaguzhinsky, L. S., & Nartsissov, Y. R. (2012). Mechanism underlying the protective effect of glycine in energetic disturbances in brain tissues under hypoxic conditions. Bulletin of experimental biology and medicine, 153(1), 44–47. https://doi.org/10.1007/s10517-012-1638-3

[765] Amin, F. U., Shah, S. A., & Kim, M. O. (2016). Glycine inhibits ethanol-induced oxidative stress, neuroinflammation and apoptotic neurodegeneration in postnatal rat brain. Neurochemistry international, 96, 1–12. https://doi.org/10.1016/j.neuint.2016.04.001

[766] Lu, Y., Zhang, J., Ma, B., Li, K., Li, X., Bai, H., Yang, Q., Zhu, X., Ben, J., & Chen, Q. (2012). Glycine attenuates cerebral ischemia/reperfusion injury by inhibiting neuronal apoptosis in mice. Neurochemistry international, 61(5), 649–658. https://doi.org/10.1016/j.neuint.2012.07.005

[767] Mori, H., Momosaki, K., Kido, J., Naramura, T., Tanaka, K., Matsumoto, S., Nakamura, K., Mitsubuchi, H., Endo, F., & Iwai, M. (2017). Amelioration by glycine of brain damage in neonatal rat brain following hypoxia-ischemia. Pediatrics international : official journal of the Japan Pediatric Society, 59(3), 321–327. https://doi.org/10.1111/ped.13164

[768] Zafra, F., Ibáñez, I., Bartolomé-Martín, D., Piniella, D., Arribas-Blázquez, M., & Giménez, C. (2017). Glycine Transporters and Its Coupling with NMDA Receptors. Advances in neurobiology, 16, 55–83. https://doi.org/10.1007/978-3-319-55769-4_4

[769] Yu, A., Alberstein, R., Thomas, A., Zimmet, A., Grey, R., Mayer, M. L., & Lau, A. Y. (2016). Molecular lock regulates binding of glycine to a primitive NMDA receptor. Proceedings of the National Academy of Sciences of the United States of America, 113(44), E6786–E6795. https://doi.org/10.1073/pnas.1607010113

[770] Li, L. J., Hu, R., Lujan, B., Chen, J., Zhang, J. J., Nakano, Y., Cui, T. Y., Liao, M. X., Chen, J. C., Man, H. Y., Feng, H., & Wan, Q. (2016). Glycine Potentiates AMPA Receptor Function through Metabotropic Activation of GluN2A-Containing NMDA Receptors. Frontiers in molecular neuroscience, 9, 102. https://doi.org/10.3389/fnmol.2016.00102

[771] Wlaź, P., & Poleszak, E. (2011). Differential effects of glycine on the anticonvulsant activity of D-cycloserine and L-701,324 in mice. Pharmacological reports : PR, 63(5), 1231–1234. https://doi.org/10.1016/s1734-1140(11)70643-0

[772] Lushnikova, I., Maleeva, G., & Skibo, G. (2018). Glycine receptors are involved in hippocampal neuronal damage caused by oxygen-glucose deficiency. Cell biology international, 42(10), 1423–1431. https://doi.org/10.1002/cbin.11034

[773] Schaefer, N., Roemer, V., Janzen, D., & Villmann, C. (2018). Impaired Glycine Receptor Trafficking in Neurological Diseases. Frontiers in Molecular Neuroscience, 11.

[774] Avila, A., Vidal, P. M., Tielens, S., Morelli, G., Laguesse, S., Harvey, R. J., Rigo, J. M., & Nguyen, L. (2014). Glycine receptors control the generation of projection neurons in the developing cerebral cortex. Cell death and differentiation, 21(11), 1696–1708. https://doi.org/10.1038/cdd.2014.75

[775] Morelli, G., Avila, A., Ravanidis, S., Aourz, N., Neve, R. L., Smolders, I., Harvey, R. J., Rigo, J. M., Nguyen, L., & Brône, B.

(2017). Cerebral Cortical Circuitry Formation Requires Functional Glycine Receptors. Cerebral cortex (New York, N.Y. : 1991), 27(3), 1863–1877. https://doi.org/10.1093/cercor/bhw025

[776] Carrasco, M., Rabaneda, L. G., Murillo-Carretero, M., Ortega-Martínez, S., Martínez-Chantar, M. L., Woodhoo, A., Luka, Z., Wagner, C., Lu, S. C., Mato, J. M., Micó, J. A., & Castro, C. (2014). Glycine N-methyltransferase expression in the hippocampus and its role in neurogenesis and cognitive performance. Hippocampus, 24(7), 840–852. https://doi.org/10.1002/hipo.22274

[777] Kodama, D., Ono, H., & Tanabe, M. (2011). Increased hippocampal glycine uptake and cognitive dysfunction after peripheral nerve injury. Pain, 152(4), 809–817. https://doi.org/10.1016/j.pain.2010.12.029

[778] Imtiaz, S., Ikram, H., Ayaz, M., Qadir, M. I., & Muhammad, S. A. (2018). Effect of glycine: Studying memory and behavioral changes in mice. Pakistan journal of pharmaceutical sciences, 31(5), 1943–1949.

[779] Banerjee, A., Ganji, S., Hulsey, K., Dimitrov, I., Maher, E., Ghose, S., Tamminga, C., & Choi, C. (2012). Measurement of glycine in gray and white matter in the human brain in vivo by 1H MRS at 7.0 T. Magnetic resonance in medicine, 68(2), 325–331. https://doi.org/10.1002/mrm.24368

[780] Huang, E. J., & Reichardt, L. F. (2001). Neurotrophins: roles in neuronal development and function. Annual review of neuroscience, 24, 677–736. https://doi.org/10.1146/annurev.neuro.24.1.677

[781] Aroeira, R. I., Vaz, S. H., Sebastião, A. M., & Valente, C. A. (2016). BDNF modulates glycine uptake in hippocampal synaptosomes by decreasing membrane insertion of glycine transporter 2. Neurochemistry international, 99, 94–102. https://doi.org/10.1016/j.neuint.2016.06.007

[782] Halagappa, V. K., Guo, Z., Pearson, M., Matsuoka, Y., Cutler, R. G., Laferla, F. M., & Mattson, M. P. (2007). Intermittent fasting and

caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiology of disease, 26(1), 212–220. https://doi.org/10.1016/j.nbd.2006.12.019

[783] Giese M, Unternaehrer E, Brand S, Calabrese P, Holsboer-Trachsler E, Eckert A (2013) The Interplay of Stress and Sleep Impacts BDNF Level. PLoS ONE 8(10): e76050. https://doi.org/10.1371/journal.pone.0076050

[784] Mattson, M. P., Duan, W., & Guo, Z. (2003). Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms. Journal of neurochemistry, 84(3), 417–431. https://doi.org/10.1046/j.1471-4159.2003.01586.x

[785] Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. Journal of psychiatric research, 60, 56–64. https://doi.org/10.1016/j.jpsychires.2014.10.003

[786] Phillips, C., Baktir, M. A., Srivatsan, M., & Salehi, A. (2014). Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. Frontiers in cellular neuroscience, 8, 170. https://doi.org/10.3389/fncel.2014.00170

[787] Fu, L., Doreswamy, V., & Prakash, R. (2014). The biochemical pathways of central nervous system neural degeneration in niacin deficiency. Neural regeneration research, 9(16), 1509–1513. https://doi.org/10.4103/1673-5374.139475

[788] Dutertre, S., Becker, C. M., & Betz, H. (2012). Inhibitory glycine receptors: an update. The Journal of biological chemistry, 287(48), 40216–40223. https://doi.org/10.1074/jbc.R112.408229

[789] Schmidt, R. W., & Thompson, M. L. (2016). Glycinergic signaling in the human nervous system: An overview of therapeutic drug targets and clinical effects. The mental health clinician, 6(6), 266–276. https://doi.org/10.9740/mhc.2016.11.266

[790] Winters, B. L., Rawling, T., Vandenberg, R. J., Christie, M. J., Bhola, R. F., & Imlach, W. L. (2018). Activity of novel lipid glycine

transporter inhibitors on synaptic signalling in the dorsal horn of the spinal cord. British journal of pharmacology, 175(12), 2337–2347. https://doi.org/10.1111/bph.14189

[791] Marshak D. W. (2016). A tale of two neurotransmitters. Visual neuroscience, 33, E017. https://doi.org/10.1017/S0952523816000146

[792] Bannai, M., Kawai, N., Nagao, K., Nakano, S., Matsuzawa, D., & Shimizu, E. (2011). Oral administration of glycine increases extracellular serotonin but not dopamine in the prefrontal cortex of rats. Psychiatry and clinical neurosciences, 65(2), 142–149. https://doi.org/10.1111/j.1440-1819.2010.02181.x

[793] Hondo, M., Furutani, N., Yamasaki, M., Watanabe, M., & Sakurai, T. (2011). Orexin neurons receive glycinergic innervations. PloS one, 6(9), e25076. https://doi.org/10.1371/journal.pone.0025076

[794] Bannai, M., & Kawai, N. (2012). New therapeutic strategy for amino acid medicine: glycine improves the quality of sleep. Journal of pharmacological sciences, 118(2), 145–148. https://doi.org/10.1254/jphs.11r04fm

[795] Costello, R. B., Lentino, C. V., Boyd, C. C., O'Connell, M. L., Crawford, C. C., Sprengel, M. L., & Deuster, P. A. (2014). The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. Nutrition journal, 13, 106. https://doi.org/10.1186/1475-2891-13-106

[796] Nelson R. F. (2012). Glycinergic neurons process images. The Journal of physiology, 590(2), 239–240. https://doi.org/10.1113/jphysiol.2011.224584

[797] Zhao, W. J., Zhang, M., Miao, Y., Yang, X. L., & Wang, Z. (2010). Melatonin potentiates glycine currents through a PLC/PKC signalling pathway in rat retinal ganglion cells. The Journal of physiology, 588(Pt 14), 2605–2619. https://doi.org/10.1113/jphysiol.2010.187641

[798] Hwang, A. D., & Peli, E. (2016). Positive and negative polarity contrast sensitivity measuring app. IS&T International Symposium on Electronic Imaging, 2016, 10.2352/ISSN.2470-1173.2016.16.HVEI-122.
[799] Xiong, W., Cheng, K., Cui, T., Godlewski, G., Rice, K. C., Xu, Y., & Zhang, L. (2011). Cannabinoid potentiation of glycine receptors contributes to cannabis-induced analgesia. Nature chemical biology, 7(5), 296–303. https://doi.org/10.1038/nchembio.552
[800] Bannai, M., Kawai, N., Ono, K., Nakahara, K., & Murakami, N. (2012). The effects of glycine on subjective daytime performance in partially sleep-restricted healthy volunteers. Frontiers in neurology, 3, 61. https://doi.org/10.3389/fneur.2012.00061
[801] McMorris, T., Harris, R. C., Swain, J., Corbett, J., Collard, K., Dyson, R. J., Dye, L., Hodgson, C., & Draper, N. (2006). Effect of creatine supplementation and sleep deprivation, with mild exercise, on cognitive and psychomotor performance, mood state, and plasma concentrations of catecholamines and cortisol. Psychopharmacology, 185(1), 93–103. https://doi.org/10.1007/s00213-005-0269-z
[802] Dworak, M., Kim, T., Mccarley, R. W., & Basheer, R. (2017). Creatine supplementation reduces sleep need and homeostatic sleep pressure in rats. Journal of sleep research, 26(3), 377–385. https://doi.org/10.1111/jsr.12523
[803] Leem, Y. H., Kato, M., & Chang, H. (2018). Regular exercise and creatine supplementation prevent chronic mild stress-induced decrease in hippocampal neurogenesis via Wnt/GSK3β/β-catenin pathway. Journal of exercise nutrition & biochemistry, 22(2), 1–6. https://doi.org/10.20463/jenb.2018.0009
[804] Brosnan, J. T., da Silva, R. P., & Brosnan, M. E. (2011). The metabolic burden of creatine synthesis. Amino acids, 40(5), 1325–1331. https://doi.org/10.1007/s00726-011-0853-y
[805] Ganguly, P., & Alam, S. F. (2015). Role of homocysteine in the development of cardiovascular disease. Nutrition journal, 14, 6.

https://doi.org/10.1186/1475-2891-14-6
[806] Si et al (2021) Epigenome-wide analysis of DNA methylation and coronary heart disease: a nested case-control study eLife 10:e68671.
[807] Wajed, S. A., Laird, P. W., & DeMeester, T. R. (2001). DNA methylation: an alternative pathway to cancer. Annals of surgery, 234(1), 10–20. https://doi.org/10.1097/00000658-200107000-00003
[808] Pittenger C. (2015). Glutamate modulators in the treatment of obsessive-compulsive disorder. Psychiatric annals, 45(6), 308–315. https://doi.org/10.3928/00485713-20150602-06
[809] Cleveland, W. L., DeLaPaz, R. L., Fawwaz, R. A., & Challop, R. S. (2009). High-dose glycine treatment of refractory obsessive-compulsive disorder and body dysmorphic disorder in a 5-year period. Neural plasticity, 2009, 768398. https://doi.org/10.1155/2009/768398
[810] Lidö, H. H., Marston, H., Ericson, M., & Söderpalm, B. (2012). The glycine reuptake inhibitor Org24598 and acamprosate reduce ethanol intake in the rat; tolerance development to acamprosate but not to Org24598. Addiction biology, 17(5), 897–907. https://doi.org/10.1111/j.1369-1600.2011.00367.x
[811] MOLANDER, A., LIDO, H. H., LOF, E., ERICSON, M., & SODERPALM, B. (2006). THE GLYCINE REUPTAKE INHIBITOR ORG 25935 DECREASES ETHANOL INTAKE AND PREFERENCE IN MALE WISTAR RATS. Alcohol and Alcoholism, 42(1), 11–18. https://doi.org/10.1093/alcalc/agl085
[812] Nic Dhonnchadha, B. Á., Pinard, E., Alberati, D., Wettstein, J. G., Spealman, R. D., & Kantak, K. M. (2012). Inhibiting glycine transporter-1 facilitates cocaine-cue extinction and attenuates reacquisition of cocaine-seeking behavior. Drug and alcohol dependence, 122(1-2), 119–126. https://doi.org/10.1016/j.drugalcdep.2011.09.017
[813] Strzelecki, D., Kropiwnicki, P., & Rabe-Jabłońska, J. (2013). Augmentacja leczenia przeciwpsychotycznego glicyna moze

zmniejszać nasilenie objawów depresyjnych oraz pozapiramidowych u chorych na schizofrenie--wyniki wstepnego 10-tygodniowego badania otwartego [Augmentation of antipsychotics with glycine may ameliorate depressive and extrapyramidal symptoms in schizophrenic patients--a preliminary 10-week open-label study]. Psychiatria polska, 47(4), 609–620.

[814] Greenwood, L. M., Leung, S., Michie, P. T., Green, A., Nathan, P. J., Fitzgerald, P., Johnston, P., Solowij, N., Kulkarni, J., & Croft, R. J. (2018). The effects of glycine on auditory mismatch negativity in schizophrenia. Schizophrenia research, 191, 61–69. https://doi.org/10.1016/j.schres.2017.05.031

[815] Yoshikawa, A., Nishimura, F., Inai, A., Eriguchi, Y., Nishioka, M., Takaya, A., Tochigi, M., Kawamura, Y., Umekage, T., Kato, K., Sasaki, T., Ohashi, Y., Iwamoto, K., Kasai, K., & Kakiuchi, C. (2018). Mutations of the glycine cleavage system genes possibly affect the negative symptoms of schizophrenia through metabolomic profile changes. Psychiatry and clinical neurosciences, 72(3), 168–179. https://doi.org/10.1111/pcn.12628

[816] Strzelecki, D., & Rabe-Jabłońska, J. (2011). Zmiana w zakresie objawów pozytywnych, negatywnych oraz psychopatologii ogólnej u pacjentów ze schizofrenia otrzymujacych augmentacje leczenia przeciwpsychotycznego glicyna: wyniki wstepnego 10-tygodniowego badania otwartego [Changes in positive and negative symptoms, general psychopathology in schizophrenic patients during augmentation of antipsychotics with glycine: a preliminary 10-week open-label study]. Psychiatria polska, 45(6), 825–837.

[817] Breitinger, U., Raafat, K. M., & Breitinger, H. G. (2015). Glucose is a positive modulator for the activation of human recombinant glycine receptors. Journal of neurochemistry, 134(6), 1055–1066. https://doi.org/10.1111/jnc.13215

[818] Breitinger, U., & Breitinger, H. G. (2016). Augmentation of glycine receptor alpha3 currents suggests a mechanism for glucose-mediated analgesia. Neuroscience letters, 612, 110–115. https://doi.org/10.1016/j.neulet.2015.11.051

[819] Purves et al (2001) 'GABA and Glycine', Neuroscience. 2nd edition., Sunderland (MA): Sinauer Associates.

[820] Hadj-Saïd, W., Fradot, V., Ivkovic, I., Sahel, J. A., Picaud, S., & Froger, N. (2017). Taurine Promotes Retinal Ganglion Cell Survival Through GABAB Receptor Activation. Advances in experimental medicine and biology, 975 Pt 2, 687–701. https://doi.org/10.1007/978-94-024-1079-2_54

[821] Bhattarai, J. P., Park, S. J., Chun, S. W., Cho, D. H., & Han, S. K. (2015). Activation of synaptic and extrasynaptic glycine receptors by taurine in preoptic hypothalamic neurons. Neuroscience letters, 608, 51–56. https://doi.org/10.1016/j.neulet.2015.10.012

[822] Kilb, W., & Fukuda, A. (2017). Taurine as an Essential Neuromodulator during Perinatal Cortical Development. Frontiers in cellular neuroscience, 11, 328. https://doi.org/10.3389/fncel.2017.00328

[823] Oja, S. S., & Saransaari, P. (2017). Significance of Taurine in the Brain. Advances in experimental medicine and biology, 975 Pt 1, 89–94. https://doi.org/10.1007/978-94-024-1079-2_8

[824] Song, N. Y., Shi, H. B., Li, C. Y., & Yin, S. K. (2012). Interaction between taurine and GABA(A)/glycine receptors in neurons of the rat anteroventral cochlear nucleus. Brain research, 1472, 1–10. https://doi.org/10.1016/j.brainres.2012.07.001

[825] Bhattarai, J. P., Cho, D. H., & Han, S. K. (2016). Activation of Strychnine-Sensitive Glycine Receptors by Shilajit on Preoptic Hypothalamic Neurons of Juvenile Mice. The Chinese journal of physiology, 59(1), 39–45. https://doi.org/10.4077/CJP.2016.BAE361

[826] Yin, H., Yang, E. J., Park, S. J., & Han, S. K. (2011). Glycine- and GABA-mimetic Actions of Shilajit on the Substantia Gelatinosa Neurons of the Trigeminal Subnucleus Caudalis in Mice. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology, 15(5), 285–289. https://doi.org/10.4196/kjpp.2011.15.5.285

[827] Cornelison, G. L., Daszkowski, A. W., Pflanz, N. C., & Mihic, S. J. (2017). Interactions between Zinc and Allosteric Modulators of the Glycine Receptor. The Journal of pharmacology and experimental therapeutics, 361(1), 1–8. https://doi.org/10.1124/jpet.116.239152

[828] Fan, D., Alamri, Y., Liu, K., MacAskill, M., Harris, P., Brimble, M., Dalrymple-Alford, J., Prickett, T., Menzies, O., Laurenson, A., Anderson, T., & Guan, J. (2018). Supplementation of Blackcurrant Anthocyanins Increased Cyclic Glycine-Proline in the Cerebrospinal Fluid of Parkinson Patients: Potential Treatment to Improve Insulin-Like Growth Factor-1 Function. Nutrients, 10(6), 714. https://doi.org/10.3390/nu10060714

[829] Rhee, S.H. et al (2009) 'Principles and clinical implications of the brain–gut–enteric microbiota axis', Nature Reviews. Gastroenterology & Hepatology, Vol 6, p 306-314.

[830] Wang, Y. and Kasper, L.H. (2014) 'The role of microbiome in central nervous system disorders', Brain Behav Immun, Vol 38, p 1-12.

[831] Carabotti, M. et al (2015) 'The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems', Annals & Gastroenterology, Vol 28(2), p 203-209.

[832] Van den Elsen, L. W., Poyntz, H. C., Weyrich, L. S., Young, W., & Forbes-Blom, E. E. (2017). Embracing the gut microbiota: the new frontier for inflammatory and infectious diseases. Clinical & Translational Immunology, 6(1), e125. doi:10.1038/cti.2016.91

[833] Lazar, V., Ditu, L.-M., Pircalabioru, G. G., Gheorghe, I., Curutiu, C., Holban, A. M., … Chifiriuc, M. C. (2018). Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer. Frontiers in Immunology, 9. doi:10.3389/fimmu.2018.01830

[834] Thaiss, C. A., Zmora, N., Levy, M., & Elinav, E. (2016). The microbiome and innate immunity. Nature, 535(7610), 65–74. doi:10.1038/nature18847

[835] Takeda S, Sato N, Morishita R (2014) Systemic inflammation, blood-brain barrier vulnerability and cognitive/non-cognitive symptoms in Alzheimer disease: relevance to pathogenesis and therapy, Front Aging Neuroscience, 6:171

[836] Arrieta, M. & Bistritz, L. & Meddings, J. (2006). Alterations in intestinal permeability. *Gut* 55 (10): 1512–1520.

[837] Mu, Q. & Kirby, J. & Reilly, C. & Luo, X. (2017). Leaky Gut As a Danger Signal for Autoimmune Diseases. *Frontiers in Immunology* 8: 598.

[838] Chen, Q., Chen, O., Martins, I. M., Hou, H., Zhao, X., Blumberg, J. B., & Li, B. (2017). Collagen peptides ameliorate intestinal epithelial barrier dysfunction in immunostimulatory Caco-2 cell monolayers via enhancing tight junctions. Food & function, 8(3), 1144–1151. https://doi.org/10.1039/c6fo01347c

[839] Sontakke, S. B., Jung, J. H., Piao, Z., & Chung, H. J. (2016). Orally Available Collagen Tripeptide: Enzymatic Stability, Intestinal Permeability, and Absorption of Gly-Pro-Hyp and Pro-Hyp. Journal of agricultural and food chemistry, 64(38), 7127–7133. https://doi.org/10.1021/acs.jafc.6b02955

[840] Zhu, S., Huang, M., Feng, G., Miao, Y., Wu, H., Zeng, M., & Lo, Y. M. (2018). Gelatin versus its two major degradation products, prolyl-hydroxyproline and glycine, as supportive therapy in experimental colitis in mice. Food science & nutrition, 6(4), 1023–1031. https://doi.org/10.1002/fsn3.639

[841] Nosworthy, M. G., & Brunton, J. A. (2016). Cysteinyl-glycine reduces mucosal proinflammatory cytokine response to fMLP in a parenterally-fed piglet model. Pediatric research, 80(2), 293–298. https://doi.org/10.1038/pr.2016.69

[842] Petrat, F., Drowatzky, J., Boengler, K., Finckh, B., Schmitz, K. J., Schulz, R., & de Groot, H. (2011). Protection from glycine at low doses in ischemia-reperfusion injury of the rat small intestine. European surgical research. Europaische chirurgische Forschung. Recherches chirurgicales europeennes, 46(4), 180–187. https://doi.org/10.1159/000324393

[843] Wang, W., Wu, Z., Lin, G., Hu, S., Wang, B., Dai, Z., & Wu, G. (2014). Glycine stimulates protein synthesis and inhibits oxidative stress in pig small intestinal epithelial cells. The Journal of nutrition, 144(10), 1540–1548. https://doi.org/10.3945/jn.114.194001

[844] Stoffels, B., Türler, A., Schmidt, J., Nazir, A., Tsukamoto, T., Moore, B. A., Schnurr, C., Kalff, J. C., & Bauer, A. J. (2011). Anti-inflammatory role of glycine in reducing rodent postoperative inflammatory ileus. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society, 23(1), 76–e8. https://doi.org/10.1111/j.1365-2982.2010.01603.x

[845] McCole D. F. (2010). The epithelial glycine transporter GLYT1: protecting the gut from inflammation. The Journal of physiology, 588(Pt 7), 1033–1034. https://doi.org/10.1113/jphysiol.2010.188516

[846] Effenberger-Neidnicht, K., Jägers, J., Verhaegh, R., & de Groot, H. (2014). Glycine selectively reduces intestinal injury during endotoxemia. The Journal of surgical research, 192(2), 592–598. https://doi.org/10.1016/j.jss.2014.06.016

[847] Howard, A., Tahir, I., Javed, S., Waring, S. M., Ford, D., & Hirst, B. H. (2010). Glycine transporter GLYT1 is essential for glycine-mediated protection of human intestinal epithelial cells against oxidative damage. The Journal of physiology, 588(Pt 6), 995–1009. https://doi.org/10.1113/jphysiol.2009.186262

[848] Howard, A., & Hirst, B. H. (2011). The glycine transporter GLYT1 in human intestine: expression and function. Biological & pharmaceutical bulletin, 34(6), 784–788. https://doi.org/10.1248/bpb.34.784

[849] Ospina-Rojas, I. C., Murakami, A. E., Oliveira, C. A., & Guerra, A. F. (2013). Supplemental glycine and threonine effects on performance, intestinal mucosa development, and nutrient utilization of growing broiler chickens. Poultry science, 92(10), 2724–2731. https://doi.org/10.3382/ps.2013-03171

[850] Moran E. T., Jr (2017). Nutrients central to maintaining intestinal absorptive efficiency and barrier integrity with fowl. Poultry science, 96(5), 1348–1363. https://doi.org/10.3382/ps/pew337

[851] Brencher, L., Petrat, F., Stych, K., Hamburger, T., & Kirsch, M. (2017). Effect of Glycine, Pyruvate, and Resveratrol on the Regeneration Process of Postischemic Intestinal Mucosa. BioMed research international, 2017, 1072969. https://doi.org/10.1155/2017/1072969

[852] Li, W., Sun, K., Ji, Y., Wu, Z., Wang, W., Dai, Z., & Wu, G. (2016). Glycine Regulates Expression and Distribution of Claudin-7 and ZO-3 Proteins in Intestinal Porcine Epithelial Cells. The Journal of nutrition, 146(5), 964–969. https://doi.org/10.3945/jn.115.228312

[853] de Aguiar Picanço, E., Lopes-Paulo, F., Marques, R. G., Diestel, C. F., Caetano, C. E., de Souza, M. V., Moscoso, G. M., & Pazos, H. M. (2011). L-arginine and glycine supplementation in the repair of the irradiated colonic wall of rats. International journal of colorectal disease, 26(5), 561–568. https://doi.org/10.1007/s00384-011-1154-3

[854] Nagahama, K., Nishio, H., Yamato, M., & Takeuchi, K. (2012). Orally administered L-arginine and glycine are highly effective against acid reflux esophagitis in rats. Medical science monitor : international medical journal of experimental and clinical research, 18(1), BR9–BR15. https://doi.org/10.12659/msm.882190

[855] Nalin, D. R., Cash, R. A., Rahman, M., & Yunus, M. (1970). Effect of glycine and glucose on sodium and water adsorption in patients with cholera. Gut, 11(9), 768–772. https://doi.org/10.1136/gut.11.9.768

[856] Craft, I. L., Geddes, D., Hyde, C. W., Wise, I. J., & Matthews, D. M. (1968). Absorption and malabsorption of glycine and glycine peptides in man. Gut, 9(4), 425–437. https://doi.org/10.1136/gut.9.4.425

[857] Akobeng, AK; Elawad, M; Gordon, M (8 February 2016). "Glutamine for induction of remission in Crohn's disease" (PDF). *Cochrane Database of Systematic Reviews*. 2: CD007348.

[858] Zhou, Q. et al. (2019). Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. *Gut* 68 (6): 996–1002.

[859] Chang, W-K. & Yang, K. & Shaio, M.-F. (1999). Effect of Glutamine on Th1 and Th2 Cytokine Responses of Human Peripheral Blood Mononuclear Cells. *Clinical Immunology* 93 (3): 294–301.

[860] Newsholme, P. (2001). Why Is L-Glutamine Metabolism Important to Cells of the Immune System in Health, Postinjury, Surgery or Infection?2. The Journal of Nutrition, 131(9), 2515S–2522S. doi:10.1093/jn/131.9.2515s

[861] Calder, P. & Yaqoob, P. (1999). Glutamine and the immune system. Amino Acids 17 (3): 227–241. Review.

[862] Tilg, H., & Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. Journal of Clinical Investigation, 121(6),

2126–2132. doi:10.1172/jci58109
[863] Drago et al (2006). Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. Scandinavian Journal of Gastroenterology, 41(4), 408–419. doi:10.1080/00365520500235334
[864] Fasano et al (2000). Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. The Lancet, 355(9214), 1518–1519. doi:10.1016/s0140-6736(00)02169-3
[865] Zarrinpar, A., Chaix, A., Yooseph, S., & Panda, S. (2014). Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. Cell metabolism, 20(6), 1006–1017. https://doi.org/10.1016/j.cmet.2014.11.008
[866] Lopez et al (2012) 'Ghrelin Prevents Disruption of the Blood–Brain Barrier after Traumatic Brain Injury', Journal of NeurotraumaVol. 29, No. 2.
[867] University of Illinois at Urbana-Champaign. (2017, December 4). Exercise changes gut microbial composition independent of diet, team reports. ScienceDaily. Retrieved May 31, 2020 from www.sciencedaily.com/releases/2017/12/171204144757.htm
[868] Gomez-Gonzalez et al (2013) 'REM Sleep Loss and Recovery Regulates Blood-Brain Barrier Function', Current Neurovascular Research, Volume 10, Number 3, 2013, pp. 197-207(11).
[869] He et al (2014). Sleep Restriction Impairs Blood-Brain Barrier Function. Journal of Neuroscience, 34(44), 14697–14706. doi:10.1523/jneurosci.2111-14.2014
[870] Haorah, J. (2005). Alcohol-induced oxidative stress in brain endothelial cells causes blood-brain barrier dysfunction. Journal of Leukocyte Biology, 78(6), 1223–1232. doi:10.1189/jlb.0605340
[871] De Filippis et al (2016). High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and

associated metabolome. Gut, 65(11), 1812–1821. https://doi.org/10.1136/gutjnl-2015-309957

[872] Layne, J. E., & Nelson, M. E. (1999). The effects of progressive resistance training on bone density: a review. Medicine and science in sports and exercise, 31(1), 25–30. https://doi.org/10.1097/00005768-199901000-00006

[873] Watson et al (2018), High-Intensity Resistance and Impact Training Improves Bone Mineral Density and Physical Function in Postmenopausal Women With Osteopenia and Osteoporosis: The LIFTMOR Randomized Controlled Trial. J Bone Miner Res, 33: 211-220.

[874] Pinheiro et al (2020) 'Evidence on physical activity and osteoporosis prevention for people aged 65+ years: a systematic review to inform the WHO guidelines on physical activity and sedentary behaviour', International Journal of Behavioral Nutrition and Physical Activity volume 17, Article number: 150.

[875] Benedetti et al (2018). The Effectiveness of Physical Exercise on Bone Density in Osteoporotic Patients. BioMed research international, 2018, 4840531. https://doi.org/10.1155/2018/4840531

[876] Zehnacker, C. H., & Bemis-Dougherty, A. (2007). Effect of weighted exercises on bone mineral density in post menopausal women. A systematic review. Journal of geriatric physical therapy (2001), 30(2), 79–88. https://doi.org/10.1519/00139143-200708000-00007

[877] Huovinen et al (2016). Bone mineral density is increased after a 16-week resistance training intervention in elderly women with decreased muscle strength, European Journal of Endocrinology, 175(6), 571-582. Retrieved Nov 26, 2022, from https://eje.bioscientifica.com/view/journals/eje/175/6/571.xml

[878] Robergs, and Roberts. (1997). Exercise Physiology: Exercise, Performance and Clinical Applications. Mosby.

[879] Yakar, S., Rosen, C. J., Beamer, W. G., Ackert-Bicknell, C. L., Wu, Y., Liu, J.-L., … LeRoith, D. (2002). Circulating levels of IGF-1

directly regulate bone growth and density. Journal of Clinical Investigation, 110(6), 771–781. doi:10.1172/jci0215463

[880] Decourtye, L., Mire, E., Clemessy, M., Heurtier, V., Ledent, T., Robinson, I. C., Mollard, P., Epelbaum, J., Meaney, M. J., Garel, S., Le Bouc, Y., & Kappeler, L. (2017). IGF-1 Induces GHRH Neuronal Axon Elongation during Early Postnatal Life in Mice. PloS one, 12(1), e0170083. https://doi.org/10.1371/journal.pone.0170083

[881] Yakar et al (2002). Circulating levels of IGF-1 directly regulate bone growth and density. The Journal of clinical investigation, 110(6), 771–781. https://doi.org/10.1172/JCI15463

[882] Yuan et al (2021). Insulin-like Growth Factor-1, Bone Mineral Density, and Fracture: A Mendelian Randomization Study. The Journal of clinical endocrinology and metabolism, 106(4), e1552–e1558. https://doi.org/10.1210/clinem/dgaa963

[883] Raisz L. G. (2005). Pathogenesis of osteoporosis: concepts, conflicts, and prospects. The Journal of clinical investigation, 115(12), 3318–3325. https://doi.org/10.1172/JCI27071

[884] Pingel et al (2012). Effects of transdermal estrogen on collagen turnover at rest and in response to exercise in postmenopausal women. Journal of applied physiology (Bethesda, Md. : 1985), 113(7), 1040–1047. https://doi.org/10.1152/japplphysiol.01463.2011

[885] Hansen et al (2009). Effect of estrogen on tendon collagen synthesis, tendon structural characteristics, and biomechanical properties in postmenopausal women. Journal of applied physiology (Bethesda, Md. : 1985), 106(4), 1385–1393.

[886] Hansen et al (2008). Ethinyl oestradiol administration in women suppresses synthesis of collagen in tendon in response to exercise. The Journal of physiology, 586(12), 3005–3016.

[887] Hansen et al (2009). Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. Journal of applied physiology

(Bethesda, Md. : 1985), 106(4), 1435–1443. https://doi.org/10.1152/japplphysiol.90933.2008

[888] Sinnesael et al (2013). Novel insights in the regulation and mechanism of androgen action on bone. Current opinion in endocrinology, diabetes, and obesity, 20(3), 240–244.

[889] Sinnesael et al (2011). Testosterone and the male skeleton: a dual mode of action. Journal of osteoporosis, 2011, 240328. https://doi.org/10.4061/2011/240328

[890] Puche, J. E., & Castilla-Cortázar, I. (2012). Human conditions of insulin-like growth factor-I (IGF-I) deficiency. Journal of translational medicine, 10, 224. https://doi.org/10.1186/1479-5876-10-224

[891] Cappola, A. R., Bandeen-Roche, K., Wand, G. S., Volpato, S., & Fried, L. P. (2001). Association of IGF-I levels with muscle strength and mobility in older women. The Journal of clinical endocrinology and metabolism, 86(9), 4139–4146. https://doi.org/10.1210/jcem.86.9.7868

[892] Noordam et al (2013). Serum insulin-like growth factor 1 and facial ageing: high levels associate with reduced skin wrinkling in a cross-sectional study. The British journal of dermatology, 168(3), 533–538. https://doi.org/10.1111/bjd.12131

[893] Zdzieblik et al (2015). Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. The British journal of nutrition, 114(8), 1237–1245.

[894] Shaw et al (2017). Vitamin C-enriched gelatin supplementation before intermittent activity augments collagen synthesis. The American journal of clinical nutrition, 105(1), 136–143.

[895] Imaoka, T., Suou, T., & Hirayama, C. (1992). A simplified gelatin tolerance test to evaluate gastric and pancreatic proteolytic activities. Research communications in chemical pathology and pharmacology, 78(1), 97–108.

[896] McAlindon et al (2011). Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. Osteoarthritis and cartilage, 19(4), 399–405.

[897] Oesser et al (1999). Oral administration of (14)C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). The Journal of nutrition, 129(10), 1891–1895. https://doi.org/10.1093/jn/129.10.1891

[898] Oesser, S., & Seifert, J. (2003). Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell and tissue research, 311(3), 393–399.

[899] Oesser et al (2007). 94 ORALLY ADMINISTERED COLLAGEN HYDROLYSATE HALTS THE PROGRESSION OF OSTEORATHRITIS IN STR/ort MICE. Osteoarthritis and Cartilage, 15.

[900] Maddalozzo, G. F., & Snow, C. M. (2000). High intensity resistance training: effects on bone in older men and women. Calcified tissue international, 66(6), 399–404.

[901] Mangine, G. T., Hoffman, J. R., Gonzalez, A. M., Townsend, J. R., Wells, A. J., Jajtner, A. R., … Stout, J. R. (2015). The effect of training volume and intensity on improvements in muscular strength and size in resistance-trained men. Physiological Reports, 3(8), e12472. doi:10.14814/phy2.12472

[902] Kraemer, W. J., Marchitelli, L., Gordon, S. E., Harman, E., Dziados, J. E., Mello, R., Frykman, P., McCurry, D., & Fleck, S. J. (1990). Hormonal and growth factor responses to heavy resistance exercise protocols. Journal of applied physiology (Bethesda, Md. : 1985), 69(4), 1442–1450. https://doi.org/10.1152/jappl.1990.69.4.1442

[903] Scudese, E., Simão, R., Senna, G., Vingren, J. L., Willardson, J. M., Baffi, M., & Miranda, H. (2016). Long Rest Interval Promotes Durable Testosterone Responses in High-Intensity Bench Press.

Journal of strength and conditioning research, 30(5), 1275–1286. https://doi.org/10.1519/JSC.0000000000001237

[904]

[905]

[906] Kato et al (2006). Effect of low-repetition jump training on bone mineral density in young women. Journal of applied physiology (Bethesda, Md. : 1985), 100(3), 839–843. https://doi.org/10.1152/japplphysiol.00666.2005

[907] Umemura, Y., Sogo, N., & Honda, A. (2002). Effects of intervals between jumps or bouts on osteogenic response to loading. Journal of applied physiology (Bethesda, Md. : 1985), 93(4), 1345–1348. https://doi.org/10.1152/japplphysiol.00358.2002

[908] Seynnes (2011). Effect of alpine skiing training on tendon mechanical properties in older men and women. Scandinavian journal of medicine & science in sports, 21 Suppl 1, 39–46.

[909] Heinemeier (2012). Uphill running improves rat Achilles tendon tissue mechanical properties and alters gene expression without inducing pathological changes. Journal of applied physiology (Bethesda, Md. : 1985), 113(5), 827–836.

[910] Jiang (2020). The effect of resistance training on serum insulin-like growth factor 1(IGF-1): A systematic review and meta-analysis. Complementary therapies in medicine, 50, 102360.

[911] Borst et al (2001). Effects of resistance training on insulin-like growth factor-I and IGF binding proteins. Medicine and science in sports and exercise, 33(4), 648–653.

[912] Arnarson (2015). Insulin-Like Growth Factor-1 and Resistance Exercise in Community Dwelling Old Adults. The journal of nutrition, health & aging, 19(8), 856–860.

[913] Sellami (2017). Combined sprint and resistance training abrogates age differences in somatotropic hormones. PloS one, 12(8), e0183184.
[914] Vestergaard et al (2012). Local administration of growth hormone stimulates tendon collagen synthesis in elderly men. Journal of applied physiology (Bethesda, Md.: 1985), 113(9), 1432–1438.
[915] Durgam et al (2012). Comparison of equine tendon- and bone marrow-derived cells cultured on tendon matrix with or without insulin-like growth factor-I supplementation. American journal of veterinary research, 73(1), 153–161.
[916] Herchenhan (2015). Insulin-like growth factor I enhances collagen synthesis in engineered human tendon tissue. Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society, 25(1), 13–19.
[917] Boesen (2013). Tendon and skeletal muscle matrix gene expression and functional responses to immobilisation and rehabilitation in young males: effect of growth hormone administration. The Journal of physiology, 591(23), 6039–6052.
[918] Hansen (2013). Local administration of insulin-like growth factor-I (IGF-I) stimulates tendon collagen synthesis in humans. Scandinavian journal of medicine & science in sports, 23(5), 614–619.
[919] Boesen (2014). Effect of growth hormone on aging connective tissue in muscle and tendon: gene expression, morphology, and function following immobilization and rehabilitation. Journal of applied physiology (Bethesda, Md. : 1985), 116(2), 192–203.
[920] Disser (2019). Insulin-like growth factor 1 signaling in tenocytes is required for adult tendon growth. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 33(11), 12680–12695.

[921] Doessing et al (2010). Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. The Journal of physiology, 588(Pt 2), 341–351.

[922] Molloy et al (2003). The roles of growth factors in tendon and ligament healing. Sports medicine (Auckland, N.Z.), 33(5), 381–394.

[923] Kjaer et al (2009). From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scandinavian journal of medicine & science in sports, 19(4), 500–510.

[924] Zhang, J., & Wang, J. H. (2013). The effects of mechanical loading on tendons--an in vivo and in vitro model study. PloS one, 8(8), e71740. https://doi.org/10.1371/journal.pone.0071740

[925] Sims et al (2007). Sodium loading aids fluid balance and reduces physiological strain of trained men exercising in the heat. Medicine and science in sports and exercise, 39(1), 123–130.

[926] Sims et al (2007). Preexercise sodium loading aids fluid balance and endurance for women exercising in the heat. Journal of applied physiology (Bethesda, Md. : 1985), 103(2), 534–541.

[927] Greenleaf JE, Looft-Wilson R, Wisherd JL, et al. Pre-exercise hypervolemia and cycle ergometer endurance in men. Biol Sport 1997;14:103-14.

[928] Coles, M. G., & Luetkemeier, M. J. (2005). Sodium-facilitated hypervolemia, endurance performance, and thermoregulation. International journal of sports medicine, 26(3), 182–187. https://doi.org/10.1055/s-2004-820989

[929] Miller, K. C., Mack, G. W., Knight, K. L., Hopkins, J. T., Draper, D. O., Fields, P. J., & Hunter, I. (2010). Reflex inhibition of electrically induced muscle cramps in hypohydrated humans. Medicine and science in sports and exercise, 42(5), 953–961. https://doi.org/10.1249/MSS.0b013e3181c0647e

[930] Bannai, M., & Kawai, N. (2012). New therapeutic strategy for amino acid medicine: glycine improves the quality of sleep. Journal of pharmacological sciences, 118(2), 145–148. https://doi.org/10.1254/jphs.11r04fm

[931] Abdul Alim et al (2018). Achilles tendon rupture healing is enhanced by intermittent pneumatic compression upregulating collagen type I synthesis. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA, 26(7), 2021–2029. https://doi.org/10.1007/s00167-017-4621-8

[932] Gould et al (2012). Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2 Suppl), e227S–e277S. https://doi.org/10.1378/chest.11-2297

[933] Loenneke et al (2015) Exercise with Blood Flow Restriction: An Updated Evidence-Based Approach for Enhanced Muscular Development. Sports Medicine, 45 (3). pp. 313-325.

[934] Yow et al (2018). Blood Flow Restriction Training After Achilles Tendon Rupture. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons, 57(3), 635–638. https://doi.org/10.1053/j.jfas.2017.11.008

[935] Garber et al (2011). Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults. Medicine & Science in Sports & Exercise, 43(7), 1334–1359. doi:10.1249/mss.0b013e318213fefb

[936] Slysz et al (2016) 'The efficacy of blood flow restricted exercise: A systematic review & meta-analysis', Journal of Science and Medicine in Sports, Volume 19, Issue 8, Pages 669–675. DOI: https://doi.org/10.1016/j.jsams.2015.09.005

[937] Ohta, H., Kurosawa, H., Ikeda, H., Iwase, Y., Satou, N., & Nakamura, S. (2003). Low-load resistance muscular training with moderate restriction of blood flow after anterior cruciate ligament

reconstruction. Acta orthopaedica Scandinavica, 74(1), 62–68. https://doi.org/10.1080/00016470310013680

[938] Takarada et al (2000) 'Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles', Medicine and Science in Sports and Exercise : December 2000 - Volume 32 - Issue 12 - p 2035-2039.

[939] Kubota, A., Sakuraba, K., Koh, S., Ogura, Y., & Tamura, Y. (2011). Blood flow restriction by low compressive force prevents disuse muscular weakness. Journal of science and medicine in sport, 14(2), 95–99. https://doi.org/10.1016/j.jsams.2010.08.007

[940] Kubota, A., Sakuraba, K., Sawaki, K., Sumide, T., & Tamura, Y. (2008). Prevention of disuse muscular weakness by restriction of blood flow. Medicine and science in sports and exercise, 40(3), 529–534. https://doi.org/10.1249/MSS.0b013e31815ddac6

[941] Fujita, S., Abe, T., Drummond, M. J., Cadenas, J. G., Dreyer, H. C., Sato, Y., Volpi, E., & Rasmussen, B. B. (2007). Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. Journal of applied physiology (Bethesda, Md. : 1985), 103(3), 903–910. https://doi.org/10.1152/japplphysiol.00195.2007

[942] Sudo, M., Ando, S., Poole, D. C., & Kano, Y. (2015). Blood flow restriction prevents muscle damage but not protein synthesis signaling following eccentric contractions. Physiological reports, 3(7), e12449. https://doi.org/10.14814/phy2.12449

[943] Loenneke, J. P., Wilson, J. M., Wilson, G. J., Pujol, T. J., & Bemben, M. G. (2011). Potential safety issues with blood flow restriction training. Scandinavian journal of medicine & science in sports, 21(4), 510–518. https://doi.org/10.1111/j.1600-0838.2010.01290.x

[944] Nakajima, T., Kurano, M., Iida, H., Takano, H., Oonuma, H., Morita, T., … KAATSU Training Group. (2006). Use and safety of KAATSU training:Results of a national survey. International Journal of KAATSU Training Research, 2(1), 5–13. doi:10.3806/ijktr.2.5

[945] Nakajima, T., Morita, T., & Sato, Y. (2011). Key considerations when conducting KAATSU training. International Journal of KAATSU Training Research, 7(1), 1–6. doi:10.3806/ijktr.7.1

[946] Bond, C. W., Hackney, K. J., Brown, S. L., & Noonan, B. C. (2019). Blood Flow Restriction Resistance Exercise as a Rehabilitation Modality Following Orthopaedic Surgery: A Review of Venous Thromboembolism Risk. The Journal of orthopaedic and sports physical therapy, 49(1), 17–27. https://doi.org/10.2519/jospt.2019.8375

[947] Calabrese, E.J., (2005). 'Paradigm lost, paradigm found: the re-emergence of hormesis as a fundamental dose response model in the toxicological sciences'. Env. Poll. 138, 379–412.

[948] Calabrese et al (2007) 'Biological Stress Response Terminology: Integrating the Concepts of Adaptive Response and Preconditioning Stress Within a Hormetic Dose-Response Framework' Toxicol Appl Pharmacol 2007 Jul 1;222(1):122-8. doi: 10.1016/j.taap.2007.02.015.

[949] Andersen et al (2011). Interleukin-6: a growth factor stimulating collagen synthesis in human tendon. Journal of applied physiology (Bethesda, Md. : 1985), 110(6), 1549–1554.

[950] Merry, T. L., & Ristow, M. (2016). Do antioxidant supplements interfere with skeletal muscle adaptation to exercise training?. The Journal of physiology, 594(18), 5135–5147.

[951] Ristow et al (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. Proceedings of the National Academy of Sciences of the United States of America, 106(21), 8665–8670. https://doi.org/10.1073/pnas.0903485106

[952] Kang et al (2020) Near-infrared-emitting nanoparticles activate collagen synthesis via TGFβ signaling. Sci Rep 10, 13309

[953] Aziz-Jalali et al (2012). Comparison of Red and Infrared Low-level Laser Therapy in the Treatment of Acne Vulgaris. Indian journal

of dermatology, 57(2), 128–130. https://doi.org/10.4103/0019-5154.94283
[954] Wunsch, A., & Matuschka, K. (2014). A controlled trial to determine the efficacy of red and near-infrared light treatment in patient satisfaction, reduction of fine lines, wrinkles, skin roughness, and intradermal collagen density increase. Photomedicine and laser surgery, 32(2), 93–100. https://doi.org/10.1089/pho.2013.3616
[955] Nam et al (2017). The Efficacy and Safety of 660 nm and 411 to 777 nm Light-Emitting Devices for Treating Wrinkles. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.], 43(3), 371–380. https://doi.org/10.1097/DSS.0000000000000981
[956] Ferraresi et al (2012). Low-level laser (light) therapy (LLLT) on muscle tissue: performance, fatigue and repair benefited by the power of light. Photonics & lasers in medicine, 1(4), 267–286. https://doi.org/10.1515/plm-2012-0032
[957] Lee et al (2006). Effects of infrared radiation on skin photo-aging and pigmentation. Yonsei medical journal, 47(4), 485–490. https://doi.org/10.3349/ymj.2006.47.4.485
[958] Gorgey, A. S., Wadee, A. N., & Sobhi, N. N. (2008). The effect of low-level laser therapy on electrically induced muscle fatigue: a pilot study. Photomedicine and laser surgery, 26(5), 501–506. https://doi.org/10.1089/pho.2007.2161
[959] Leal Junior, E. C., Lopes-Martins, R. A., Dalan, F., Ferrari, M., Sbabo, F. M., Generosi, R. A., Baroni, B. M., Penna, S. C., Iversen, V. V., & Bjordal, J. M. (2008). Effect of 655-nm low-level laser therapy on exercise-induced skeletal muscle fatigue in humans. Photomedicine and laser surgery, 26(5), 419–424. https://doi.org/10.1089/pho.2007.2160
[960] Gale, G. D., Rothbart, P. J., & Li, Y. (2006). Infrared therapy for chronic low back pain: a randomized, controlled trial. Pain research & management, 11(3), 193–196. https://doi.org/10.1155/2006/876920

[961] Bjordal, J. M., Couppé, C., Chow, R. T., Tunér, J., & Ljunggren, E. A. (2003). A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. The Australian journal of physiotherapy, 49(2), 107–116. https://doi.org/10.1016/s0004-9514(14)60127-6

[962] de Paula Gomes, C., Leal-Junior, E., Dibai-Filho, A. V., de Oliveira, A. R., Bley, A. S., Biasotto-Gonzalez, D. A., & de Tarso Camillo de Carvalho, P. (2018). Incorporation of photobiomodulation therapy into a therapeutic exercise program for knee osteoarthritis: A placebo-controlled, randomized, clinical trial. Lasers in surgery and medicine, 50(8), 819–828. https://doi.org/10.1002/lsm.22939

[963] Angelova, A., & Ilieva, E. M. (2016). Effectiveness of High Intensity Laser Therapy for Reduction of Pain in Knee Osteoarthritis. Pain research & management, 2016, 9163618. https://doi.org/10.1155/2016/9163618

[964] NASA (2011) 'NASA Light Technology Successfully Reduces Cancer Patients Painful Side Effects from Radiation and Chemotherapy', Accessed Online: https://www.nasa.gov/topics/nasalife/features/heals.html

[965] Hu, D., Zhu, S., & Potas, J. R. (2016). Red LED photobiomodulation reduces pain hypersensitivity and improves sensorimotor function following mild T10 hemicontusion spinal cord injury. Journal of neuroinflammation, 13(1), 200. https://doi.org/10.1186/s12974-016-0679-3

[966] Huang, Z., Ma, J., Chen, J., Shen, B., Pei, F., & Kraus, V. B. (2015). The effectiveness of low-level laser therapy for nonspecific chronic low back pain: a systematic review and meta-analysis. Arthritis research & therapy, 17, 360. https://doi.org/10.1186/s13075-015-0882-0

[967] Chow, R. T., Johnson, M. I., Lopes-Martins, R. A., & Bjordal, J. M. (2009). Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. Lancet (London,

England), 374(9705), 1897–1908. https://doi.org/10.1016/S0140-6736(09)61522-1
[968] Brassolatti, P., de Andrade, A., Bossini, P. S., Otterço, A. N., & Parizotto, N. A. (2018). Evaluation of the low-level laser therapy application parameters for skin burn treatment in experimental model: a systematic review. Lasers in medical science, 33(5), 1159–1169. https://doi.org/10.1007/s10103-018-2526-5
[969] Gál, P., Stausholm, M. B., Kováč, I., Dosedla, E., Luczy, J., Sabol, F., & Bjordal, J. M. (2018). Should open excisions and sutured incisions be treated differently? A review and meta-analysis of animal wound models following low-level laser therapy. Lasers in medical science, 33(6), 1351–1362. https://doi.org/10.1007/s10103-018-2496-7
[970] Güngörmüş, M., & Akyol, U. (2009). The effect of gallium-aluminum-arsenide 808-nm low-level laser therapy on healing of skin incisions made using a diode laser. Photomedicine and laser surgery, 27(6), 895–899. https://doi.org/10.1089/pho.2008.2431
[971] Fiório, F. B., Silveira, L., Jr, Munin, E., de Lima, C. J., Fernandes, K. P., Mesquita-Ferrari, R. A., de Carvalho, P., Lopes-Martins, R. A., Aimbire, F., & de Carvalho, R. A. (2011). Effect of incoherent LED radiation on third-degree burning wounds in rats. Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology, 13(6), 315–322. https://doi.org/10.3109/14764172.2011.630082
[972] Fiório, F. B., Silveira, L., Jr, Munin, E., de Lima, C. J., Fernandes, K. P., Mesquita-Ferrari, R. A., de Carvalho, P., Lopes-Martins, R. A., Aimbire, F., & de Carvalho, R. A. (2011). Effect of incoherent LED radiation on third-degree burning wounds in rats. Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology, 13(6), 315–322. https://doi.org/10.3109/14764172.2011.630082
[973] Brassolatti, P., de Andrade, A., Bossini, P. S., Otterço, A. N., & Parizotto, N. A. (2018). Evaluation of the low-level laser therapy application parameters for skin burn treatment in experimental

model: a systematic review. Lasers in medical science, 33(5), 1159–1169. https://doi.org/10.1007/s10103-018-2526-5

[974] Avci, P., Gupta, A., Sadasivam, M., Vecchio, D., Pam, Z., Pam, N., & Hamblin, M. R. (2013). Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring. Seminars in cutaneous medicine and surgery, 32(1), 41–52.

[975] Al-Watban F. A. (2009). Laser therapy converts diabetic wound healing to normal healing. Photomedicine and laser surgery, 27(1), 127–135. https://doi.org/10.1089/pho.2008.2406

[976] Karu, T. I., & Afanas'eva, N. I. (1995). [Cytochrome c oxidase as the primary photoacceptor upon laser exposure of cultured cells to visible and near IR-range light]. Doklady Akademii nauk, 342(5), 693–695.

[977] Karu T. I. (2010). Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. IUBMB life, 62(8), 607–610. https://doi.org/10.1002/iub.359

[978] Salehpour, F., Mahmoudi, J., Kamari, F., Sadigh-Eteghad, S., Rasta, S. H., & Hamblin, M. R. (2018). Brain Photobiomodulation Therapy: a Narrative Review. Molecular neurobiology, 55(8), 6601–6636. https://doi.org/10.1007/s12035-017-0852-4

[979] Karu, T. I., Pyatibrat, L. V., & Afanasyeva, N. I. (2005). Cellular effects of low power laser therapy can be mediated by nitric oxide. Lasers in surgery and medicine, 36(4), 307–314. https://doi.org/10.1002/lsm.20148

[980] Greco, M., Guida, G., Perlino, E., Marra, E., & Quagliariello, E. (1989). Increase in RNA and protein synthesis by mitochondria irradiated with helium-neon laser. Biochemical and biophysical research communications, 163(3), 1428–1434. https://doi.org/10.1016/0006-291x(89)91138-8

[981] Prindeze, N. J., Moffatt, L. T., & Shupp, J. W. (2012). Mechanisms of action for light therapy: a review of molecular interactions. Experimental biology and medicine (Maywood, N.J.), 237(11), 1241–1248. https://doi.org/10.1258/ebm.2012.012180

[982] Ferraresi, C., Hamblin, M. R., & Parizotto, N. A. (2012). Low-level laser (light) therapy (LLLT) on muscle tissue: performance, fatigue and repair benefited by the power of light. Photonics & lasers in medicine, 1(4), 267–286. https://doi.org/10.1515/plm-2012-0032

[983] Møller, K.I., Kongshoj, B., Philipsen, P.A., Thomsen, V.O. and Wulf, H.C. (2005), How Finsen's light cured lupus vulgaris. Photodermatology, Photoimmunology & Photomedicine, 21: 118-124. https://doi.org/10.1111/j.1600-0781.2005.00159.x

[984] The Nobel Prize in Physiology or Medicine 1903. NobelPrize.org. Nobel Prize Outreach AB 2021. Tue. 3 Aug 2021. <https://www.nobelprize.org/prizes/medicine/1903/summary/>

[985] Chung, H., Dai, T., Sharma, S. K., Huang, Y. Y., Carroll, J. D., & Hamblin, M. R. (2012). The nuts and bolts of low-level laser (light) therapy. Annals of biomedical engineering, 40(2), 516–533. https://doi.org/10.1007/s10439-011-0454-7

[986] Bjordal, J. M., Lopes-Martins, R. A., Joensen, J., Couppe, C., Ljunggren, A. E., Stergioulas, A., & Johnson, M. I. (2008). A systematic review with procedural assessments and meta-analysis of low level laser therapy in lateral elbow tendinopathy (tennis elbow). BMC musculoskeletal disorders, 9, 75. https://doi.org/10.1186/1471-2474-9-75

[987] Denda, M., & Fuziwara, S. (2008). Visible radiation affects epidermal permeability barrier recovery: selective effects of red and blue light. The Journal of investigative dermatology, 128(5), 1335–1336. https://doi.org/10.1038/sj.jid.5701168

[988] Hasten, DL. et al (2000) 'Resistance exercise acutely increases MHC and mixed muscle protein synthesis rates in 78-84 and 23-32 yr olds', Americal Journal of Physiology. Endocrinology and Metabolism, Vol 278(4), E620-626.

[989] West, DW. et al (2011) 'Rapid aminoacidemia enhances myofibrillar protein synthesis and anabolic intramuscular signaling responses after resistance exercise', Americal Journal of Clinical Nutrition, Vol 94(3), p 795-803.

[990] Wikipedia (2022) ‘Gelatin’, Accessed Online November 30th 2022: https://en.wikipedia.org/wiki/Gelatin

[991] Poppe, J. (1997). Gelatin, in A. Imeson (ed.) Thickening and Gelling Agents for Food (2nd ed.): 144–68. London: Blackie Academic and Professional.

[992] EASTOE J. E. (1955). The amino acid composition of mammalian collagen and gelatin. The Biochemical journal, 61(4), 589–600. https://doi.org/10.1042/bj0610589

[993] Alcock, R. D., Shaw, G. C., & Burke, L. M. (2019). Bone Broth Unlikely to Provide Reliable Concentrations of Collagen Precursors Compared With Supplemental Sources of Collagen Used in Collagen Research, International Journal of Sport Nutrition and Exercise Metabolism, 29(3), 265-272. Retrieved Nov 1, 2022, from https://journals.humankinetics.com/view/journals/ijsnem/29/3/article-p265.xml

[994] Alcock et al (2019). Bone Broth Unlikely to Provide Reliable Concentrations of Collagen Precursors Compared With Supplemental Sources of Collagen Used in Collagen Research. International journal of sport nutrition and exercise metabolism, 29(3), 265–272. https://doi.org/10.1123/ijsnem.2018-0139

[995] Alcock (2019). Bone Broth Unlikely to Provide Reliable Concentrations of Collagen Precursors Compared With Supplemental Sources of Collagen Used in Collagen Research. International journal of sport nutrition and exercise metabolism, 29(3), 265–272.

[996] Rennard (2000). Chicken soup inhibits neutrophil chemotaxis in vitro. Chest, 118(4), 1150–1157. https://doi.org/10.1378/chest.118.4.1150

[997] Domínguez-Rodrigo, M. (2002). Hunting and Scavenging by Early Humans: The State of the Debate. Journal of World Prehistory, 16(1), 1–54. http://www.jstor.org/stable/25801183

[998] Hsu et al (2017). Essential and toxic metals in animal bone broths. Food & nutrition research, 61(1), 1347478. https://doi.org/10.1080/16546628.2017.1347478

[999] Medindia (2022) 'Glycine Rich Foods', Accessed Online Nov 28th 2022: https://www.medindia.net/nutrition-data/nutrients/glycine-rich-foods.htm

[1000] Arnarson (2019) 'Methionine vs. Glycine — Is Too Much Muscle Meat Bad?', Healthline, Accessed Online November 6th 2022: https://www.healthline.com/nutrition/methionine-vs-glycine#what-they-are

[1001] Masterjohn 'Balancing Methionine and Glycine in Foods: The Database', Accessed Online November 6th 2022: https://chrismasterjohnphd.com/blog/balancing-methionine-and-glycine-in-foods-the-database

[1002] Medindia (2022) 'Methionine Rich Foods', Accessed Online Nov 28th 2022: https://www.medindia.net/nutrition-data/nutrients/methionine-rich-foods.htm

[1003] Arnarson (2019) 'Methionine vs. Glycine — Is Too Much Muscle Meat Bad?', Healthline, Accessed Online November 6th 2022: https://www.healthline.com/nutrition/methionine-vs-glycine#what-they-are

[1004] Cappola et al (2001). Association of IGF-I levels with muscle strength and mobility in older women. The Journal of clinical endocrinology and metabolism, 86(9), 4139–4146. https://doi.org/10.1210/jcem.86.9.7868

[1005] Puche, J. E., & Castilla-Cortázar, I. (2012). Human conditions of insulin-like growth factor-I (IGF-I) deficiency. Journal of translational medicine, 10, 224. https://doi.org/10.1186/1479-5876-10-224

[1006] Svensson et al (2012). Both low and high serum IGF-I levels associate with cancer mortality in older men. The Journal of

clinical endocrinology and metabolism, 97(12), 4623–4630. https://doi.org/10.1210/jc.2012-2329

[1007] Burgers et al (2011). Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. The Journal of clinical endocrinology and metabolism, 96(9), 2912–2920. https://doi.org/10.1210/jc.2011-1377

[1008] Wood et al (2009). Senile hair graying: H2O2-mediated oxidative stress affects human hair color by blunting methionine sulfoxide repair. FASEB journal : official publication of the Federation of American Societies for Experimental Biology, 23(7), 2065–2075.

[1009] Gao et al (2018). S-Adenosyl Methionine and Transmethylation Pathways in Neuropsychiatric Diseases Throughout Life. Neurotherapeutics, 15(1), 156–175.

[1010] Medindia (2022) 'Hydroxyproline Rich Foods', Accessed Online Nov 28th 2022: https://www.medindia.net/nutrition-data/nutrients/hydroxyproline-rich-foods.htm

[1011] Eat This Much Inc (2022) 'High hydroxyproline foods', Accessed Online Nov 28th 2022: https://www.eatthismuch.com/food/browse/high-hydroxyproline-foods/?q=&type=food&order_by=-hydroxyproline&show_nutrient=hydroxyproline&nutrition_display=

[1012] Medindia (2022) 'Hydroxyproline Rich Foods', Accessed Online Nov 28th 2022: https://www.medindia.net/nutrition-data/nutrients/hydroxyproline-rich-foods.htm

[1013] Eat This Much Inc (2022) 'High hydroxyproline foods', Accessed Online Nov 28th 2022: https://www.eatthismuch.com/food/browse/high-hydroxyproline-foods/?q=&type=food&order_by=-hydroxyproline&show_nutrient=hydroxyproline&nutrition_display=

[1014] Borer K. T. (2005). Physical activity in the prevention and amelioration of osteoporosis in women : interaction of mechanical, hormonal and dietary factors. Sports medicine (Auckland, N.Z.), 35(9), 779–830. https://doi.org/10.2165/00007256-200535090-00004

[1015] Office of the Federal Register, Government Publishing Office. §101.72 Food labeling: health claims: calcium, vitamin D, and osteoporosis. Electronic Code of Federal Regulations, Title 21: Food and Drugs.

[1016] Tai, V., Leung, W., Grey, A., Reid, I. R., & Bolland, M. J. (2015). Calcium intake and bone mineral density: systematic review and meta-analysis. BMJ (Clinical research ed.), 351, h4183. https://doi.org/10.1136/bmj.h4183

[1017] Bolland, M. J., Leung, W., Tai, V., Bastin, S., Gamble, G. D., Grey, A., & Reid, I. R. (2015). Calcium intake and risk of fracture: systematic review. BMJ (Clinical research ed.), 351, h4580. https://doi.org/10.1136/bmj.h4580

[1018] Chung, M., Lee, J., Terasawa, T., Lau, J., & Trikalinos, T. A. (2011). Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Annals of internal medicine, 155(12), 827–838. https://doi.org/10.7326/0003-4819-155-12-201112200-00005

[1019] Cosman, F., de Beur, S. J., LeBoff, M. S., Lewiecki, E. M., Tanner, B., Randall, S., Lindsay, R., & National Osteoporosis Foundation (2014). Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 25(10), 2359–2381. https://doi.org/10.1007/s00198-014-2794-2

[1020] Lind, L., Skarfors, E., Berglund, L., Lithell, H., & Ljunghall, S. (1997). Serum calcium: A new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. Journal of Clinical Epidemiology, 50(8), 967–973. doi:10.1016/s0895-4356(97)00104-2

[1021] McKane, W. R., Khosla, S., Egan, K. S., Robins, S. P., Burritt, M. F., & Riggs, B. L. (1996). Role of calcium intake in modulating age-related increases in parathyroid function and bone

resorption. The Journal of Clinical Endocrinology & Metabolism, 81(5), 1699–1703. doi:10.1210/jcem.81.5.8626819

[1022] NIH (2020) 'Calcium: Fact Sheet for Health Professionals', Dietary Supplement Fact Sheets, Accessed Online Jan 26 2021: https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/

[1023] Puigdellivol et al (2018). Effectiveness of a Dietary Supplement Containing Hydrolyzed Collagen, Chondroitin Sulfate, and Glucosamine in Pain Reduction and Functional Capacity in Osteoarthritis Patients. Journal of Dietary Supplements, 16(4), 379–389.

[1024] Inoue et al (2016). Ingestion of bioactive collagen hydrolysates enhance facial skin moisture and elasticity and reduce facial ageing signs in a randomised double-blind placebo-controlled clinical study. Journal of the science of food and agriculture, 96(12), 4077–4081.

[1025] Sibilla and Borumand (2015) 'Effects of a nutritional supplement containing collagen peptides on skin elasticity, hydration and wrinkles', Journal of Medical Nutrition and Nutraceuticals 4(1):47.

[1026] Proksch et al (2014). Oral supplementation of specific collagen peptides has beneficial effects on human skin physiology: a double-blind, placebo-controlled study. Skin pharmacology and physiology, 27(1), 47–55. https://doi.org/10.1159/000351376

[1027] Trookman et al (2009). Immediate and Long-term Clinical Benefits of a Topical Treatment for Facial Lines and Wrinkles. The Journal of clinical and aesthetic dermatology, 2(3), 38–43.

[1028] Schepetkin et al (2015). Anti-Inflammatory Effects and Joint Protection in Collagen-Induced Arthritis after Treatment with IQ-1S, a Selective c-Jun N-Terminal Kinase Inhibitor. The Journal of pharmacology and experimental therapeutics, 353(3), 505–516.

[1029] Bello, A. E., & Oesser, S. (2006). Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature. Current medical research and opinion, 22(11), 2221–2232. https://doi.org/10.1185/030079906X148373

[1030] Silva (2014). Marine origin collagens and its potential applications. Marine drugs, 12(12), 5881–5901.
[1031] Sikorski et al (1984). The role of collagen in the quality and processing of fish. Critical reviews in food science and nutrition, 20(4), 301–343. https://doi.org/10.1080/10408398409527393
[1032] Sikorski et al (1984). The role of collagen in the quality and processing of fish. Critical reviews in food science and nutrition, 20(4), 301–343. https://doi.org/10.1080/10408398409527393
[1033] Fan, J., Zhuang, Y., & Li, B. (2013). Effects of collagen and collagen hydrolysate from jellyfish umbrella on histological and immunity changes of mice photoaging. Nutrients, 5(1), 223–233.
[1034] Ngo, D. H., & Kim, S. K. (2013). Marine bioactive peptides as potential antioxidants. Current protein & peptide science, 14(3), 189–198. https://doi.org/10.2174/1389203711314999004 1
[1035] Sano, A. (2003). Atelocollagen for protein and gene delivery. Advanced Drug Delivery Reviews, 55(12), 1651–1677. https://doi.org/10.1016/j.addr.2003.08.005
[1036] De Luca et al (2016). Skin Antiageing and Systemic Redox Effects of Supplementation with Marine Collagen Peptides and Plant-Derived Antioxidants: A Single-Blind Case-Control Clinical Study. Oxidative medicine and cellular longevity, 2016, 4389410. https://doi.org/10.1155/2016/4389410
[1037] Senaratne et al (2006). Isolation and characterization of collagen from brown backed toadfish (Lagocephalus gloveri) skin. Bioresource Technology, 97(2), 191–197. https://doi.org/10.1016/j.biortech.2005.02.024
[1038] Shahidi, F. (1994) Seafoods: Chemistry, Processing, Technology and Quality. Blackie Academic and Professional, Glasgow.
[1039] Asai et al (2019). Food-Derived Collagen Peptides, Prolyl-Hydroxyproline (Pro-Hyp), and Hydroxyprolyl-Glycine (Hyp-Gly)

Enhance Growth of Primary Cultured Mouse Skin Fibroblast Using Fetal Bovine Serum Free from Hydroxyprolyl Peptide. International journal of molecular sciences, 21(1), 229. https://doi.org/10.3390/ijms21010229

[1040] Shigemura et al (2011). Identification of a novel food-derived collagen peptide, hydroxyprolyl-glycine, in human peripheral blood by pre-column derivatisation with phenyl isothiocyanate. Food chemistry, 129(3), 1019–1024. https://doi.org/10.1016/j.foodchem.2011.05.066

[1041] Kitakaze et al (2016). The collagen derived dipeptide hydroxyprolyl-glycine promotes C2C12 myoblast differentiation and myotube hypertrophy. Biochemical and biophysical research communications, 478(3), 1292–1297. https://doi.org/10.1016/j.bbrc.2016.08.114

[1042] Shimizu et al (2015). Oral collagen-derived dipeptides, prolyl-hydroxyproline and hydroxyprolyl-glycine, ameliorate skin barrier dysfunction and alter gene expression profiles in the skin. Biochemical and biophysical research communications, 456(2), 626–630. https://doi.org/10.1016/j.bbrc.2014.12.006

[1043] Asai (2019). Food-Derived Collagen Peptides, Prolyl-Hydroxyproline (Pro-Hyp), and Hydroxyprolyl-Glycine (Hyp-Gly) Enhance Growth of Primary Cultured Mouse Skin Fibroblast Using Fetal Bovine Serum Free from Hydroxyprolyl Peptide. International Journal of Molecular Sciences, 21(1), 229. https://doi.org/10.3390/ijms21010229

[1044] Ruff et al (2009). Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. Clinical interventions in aging, 4, 235–240. https://doi.org/10.2147/cia.s5797

[1045] Kiers, J. L., & Bult, J. (2021). Mildly Processed Natural Eggshell Membrane Alleviates Joint Pain Associated with Osteoarthritis of the Knee: A Randomized Double-Blind Placebo-Controlled Study. Journal of medicinal food, 24(3), 292–298. https://doi.org/10.1089/jmf.2020.0034

[1046] Hewlings, S., Kalman, D., & Schneider, L. V. (2019). A Randomized, Double-Blind, Placebo-Controlled, Prospective Clinical Trial Evaluating Water-Soluble Chicken Eggshell Membrane for Improvement in Joint Health in Adults with Knee Osteoarthritis. Journal of medicinal food, 22(9), 875–884. https://doi.org/10.1089/jmf.2019.0068

[1047] Ruff, K. J., Winkler, A., Jackson, R. W., DeVore, D. P., & Ritz, B. W. (2009). Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study. Clinical rheumatology, 28(8), 907–914. https://doi.org/10.1007/s10067-009-1173-4

[1048] Ruff, K. J., DeVore, D. P., Leu, M. D., & Robinson, M. A. (2009). Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. Clinical interventions in aging, 4, 235–240. https://doi.org/10.2147/cia.s5797

[1049] Ruff, K. J., Morrison, D., Duncan, S. A., Back, M., Aydogan, C., & Theodosakis, J. (2018). Beneficial effects of natural eggshell membrane versus placebo in exercise-induced joint pain, stiffness, and cartilage turnover in healthy, postmenopausal women. Clinical interventions in aging, 13, 285–295. https://doi.org/10.2147/CIA.S153782

[1050] Ohto-Fujita et al (2011). Hydrolyzed eggshell membrane immobilized on phosphorylcholine polymer supplies extracellular matrix environment for human dermal fibroblasts. Cell and tissue research, 345(1), 177–190. https://doi.org/10.1007/s00441-011-1172-z

[1051] Yoo, J., Park, K., Yoo, Y., Kim, J., Yang, H., & Shin, Y. (2014). Effects of Egg Shell Membrane Hydrolysates on Anti-Inflammatory, Anti-Wrinkle, Anti-Microbial Activity and Moisture-Protection. Korean journal for food science of animal resources, 34(1), 26–32. https://doi.org/10.5851/kosfa.2014.34.1.26

[1052] Kalman, D. S., & Hewlings, S. (2020). The effect of oral hydrolyzed eggshell membrane on the appearance of hair, skin, and nails in healthy middle-aged adults: A randomized double-blind placebo-controlled clinical trial. Journal of cosmetic dermatology, 19(6), 1463–1472. https://doi.org/10.1111/jocd.13275

[1053] Ruff et al (2012). Safety evaluation of a natural eggshell membrane-derived product. Food and Chemical Toxicology, 50(3–4), 604–611. https://doi.org/10.1016/j.fct.2011.12.036

[1054] Wong et al (1984). Collagen in the egg shell membranes of the hen. Developmental biology, 104(1), 28–36. https://doi.org/10.1016/0012-1606(84)90033-2

[1055] Brauner, P., Klug, K., & Jäckel, U. (2016). Eggshells as a source for occupational exposure to airborne bacteria in hatcheries. Journal of occupational and environmental hygiene, 13(12), 950–959. https://doi.org/10.1080/15459624.2016.1200192

[1056] Pande et al (2016). Salmonella enterica isolates from layer farm environments are able to form biofilm on eggshell surfaces. Biofouling, 32(7), 699–710.

[1057] Peterkofsky B. (1991). Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. The American journal of clinical nutrition, 54(6 Suppl), 1135S–1140S. https://doi.org/10.1093/ajcn/54.6.1135s

[1058] NIH (2021) 'Vitamin C', Fact Sheet for Health Professionals: Accessed Online November 16th 2022: https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/

[1059] NIH (2020) 'Copper: Fact Sheet for Health Professionals', Dietary Supplement Fact Sheets, Accessed Online Dec 9 2020: https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/

[1060] Lurie et al (1989) 'The copper content of foods based on a critical evaluation of published analytical data'. J Food Comp Anal 2:298–316.

[1061] SELF Nutrition Data (2018) 'Foods highest in Copper', Accessed Online Dec 9 2020: https://nutritiondata.self.com/foods-000125000000000000000-w.html

[1062] Sandstead, H. H., & Shepard, G. H. (1968). The effect of zinc deficiency on the tensile strength of healing surgical incisions in the integument of the rat. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.), 128(3), 687–689. https://doi.org/10.3181/00379727-128-33100

[1063] Sandstead, H. H., Lanier, V. C., Jr, Shephard, G. H., & Gillespie, D. D. (1970). Zinc and wound healing. Effects of zinc deficiency and zinc supplementation. The American journal of clinical nutrition, 23(5), 514–519. https://doi.org/10.1093/ajcn/23.5.514

[1064] Pories, W. J., Henzel, J. H., Rob, C. G., & Strain, W. H. (1967). Acceleration of healing with zinc sulfate. Annals of surgery, 165(3), 432–436. https://doi.org/10.1097/00000658-196703000-00015

[1065] Brodribb and Ricketts (1972) 'The effect of zinc in the healing of burns', Injury, Volume 3, Issue 1, 1972, Pages 25-29, https://doi.org/10.1016/S0020-1383(71)80132-8

[1066] Han, B., Fang, W. H., Zhao, S., Yang, Z., & Hoang, B. X. (2020). Zinc sulfide nanoparticles improve skin regeneration. Nanomedicine: Nanotechnology, Biology and Medicine, 29, 102263. doi:10.1016/j.nano.2020.102263

[1067] Tengrup, I., Ahonen, J., & Zederfeldt, B. (1981). Influence of zinc on synthesis and the accumulation of collagen in early granulation tissue. Surgery, gynecology & obstetrics, 152(3), 323–326.

[1068] Latafat Husain, S. (1969). ORAL ZINC SULPHATE IN LEG ULCERS. The Lancet, 293(7605), 1069–1071. doi:10.1016/s0140-6736(69)91706-1

[1069] Momen-Heravi, M., Barahimi, E., Razzaghi, R., Bahmani, F., Gilasi, H. R., & Asemi, Z. (2017). The effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Wound Repair and Regeneration, 25(3), 512–520. doi:10.1111/wrr.12537

[1070] Greaves, M. W., & Skillen, A. W. (1970). Effects of long-continued ingestion of zinc sulphate in patients with venous leg ulceration. Lancet (London, England), 2(7679), 889–891. https://doi.org/10.1016/s0140-6736(70)92066-0

[1071] Serjeant, G., Galloway, R., & Gueri, M. (1970). ORAL ZINC SULPHATE IN SICKLE-CELL ULCERS. The Lancet, 296(7679), 891–893. doi:10.1016/s0140-6736(70)92067-2

[1072] Nakamura, H., Sekiguchi, A., Ogawa, Y., Kawamura, T., Akai, R., Iwawaki, T., … Motegi, S. (2019). Zinc deficiency exacerbates pressure ulcers by increasing oxidative stress and ATP in the skin. Journal of Dermatological Science, 95(2), 62–69. doi:10.1016/j.jdermsci.2019.07.004

[1073] Seo, H. J., Cho, Y. E., Kim, T., Shin, H. I., & Kwun, I. S. (2010). Zinc may increase bone formation through stimulating cell proliferation, alkaline phosphatase activity and collagen synthesis in osteoblastic MC3T3-E1 cells. Nutrition research and practice, 4(5), 356–361. https://doi.org/10.4162/nrp.2010.4.5.356

[1074] Fernandez-Madrid, F., Prasad, A. S., & Oberleas, D. (1971). Effect of zinc deficiency on collagen metabolism. The Journal of laboratory and clinical medicine, 78(5), 853.

[1075] Hoekstra W. G. (1969). Skeletal and skin lesions of zinc-deficiency chickens and swine. Possible relationship to "connective tissue diseases" of man. The American journal of clinical nutrition, 22(9), 1268–1277. https://doi.org/10.1093/ajcn/22.9.1268

[1076] Yuzbasiyan-Gurkan, V., Grider, A., Nostrant, T., Cousins, R. J., & Brewer, G. J. (1992). Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. The Journal of laboratory and clinical medicine, 120(3), 380–386.

[1077] Fox P. L. (2003). The copper-iron chronicles: the story of an intimate relationship. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine, 16(1), 9–40. https://doi.org/10.1023/a:1020799512190

[1078] Fischer, P. W., Giroux, A., & L'Abbé, M. R. (1984). Effect of zinc supplementation on copper status in adult man. The American Journal of Clinical Nutrition, 40(4), 743–746. doi:10.1093/ajcn/40.4.743

[1079] Yadrick, M. K., Kenney, M. A., & Winterfeldt, E. A. (1989). Iron, copper, and zinc status: response to supplementation with zinc or zinc and iron in adult females. The American Journal of Clinical Nutrition, 49(1), 145–150. doi:10.1093/ajcn/49.1.145

[1080] U.S. Department of Agriculture (2019), 'Agricultural Research Service'. Food Data Central.

[1081] NIH (2020) 'Zinc: Fact Sheet for Health Professionals', Dietary Supplement Fact Sheets, Accessed Online Dec 10 2020: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

[1082] Whitbread (2020) 'Top 10 Foods Highest in Zinc', My Food Data, Accessed Online Dec 10 2020: https://www.myfooddata.com/articles/high-zinc-foods.php

[1083] Hall, I., Chen, S., Rajendran, K., Sood, A., Spielvogel, B., & Shih, J. (1994). Hypolipidemic, Anti-Obesity, Anti-Inflammatory, Anti-Osteoporotic, and Anti-Neoplastic Properties of Amine Carboxyboranes. Environmental Health Perspectives, 102, 21-30. doi:10.2307/3431958

[1084] Meacham, S. L., Taper, L. J., & Volpe, S. L. (1995). Effect of boron supplementation on blood and urinary calcium, magnesium, and phosphorus, and urinary boron in athletic and sedentary women. The American Journal of Clinical Nutrition, 61(2), 341–345. doi:10.1093/ajcn/61.2.341

[1085] WILSON, J. H., & RUSZLER, P. L. (1998). Long term effects of boron on layer bone strength and production parameters. British Poultry Science, 39(1), 11–15. doi:10.1080/00071669889312

[1086] Travers, R. L., Rennie, G. C., & Newnham, R. E. (1990). Boron and Arthritis: The Results of a Double-blind Pilot Study. Journal of Nutritional Medicine, 1(2), 127–132. doi:10.3109/13590849009003147

[1087] Newnham RE. How boron is being used in medical practice. In: Goldbach HE, Rerkasem B, Wimmer MA, Brown PH, Thellier M, Bell RW, eds. Boron in Plant and Animal Nutrition. New York, NY: Kluwer Academic/Plenum; 2002:59-62.

[1088] Newnham R. E. (1994). Essentiality of boron for healthy bones and joints. Environmental health perspectives, 102 Suppl 7(Suppl 7), 83–85. https://doi.org/10.1289/ehp.94102s783

[1089] Dupre, J. N., Keenan, M. J., Hegsted, M., & Brudevold, A. M. (1994). Effects of dietary boron in rats fed a vitamin D-deficient diet. Environmental health perspectives, 102 Suppl 7(Suppl 7), 55–58. https://doi.org/10.1289/ehp.94102s755

[1090] Nielsen, F. H, Mullen, L. M, & Gallagher, S. K. (1990). Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a magnesium-low diet. Journal of trace elements in experimental medicine, 3, 45.

[1091] Nielsen, F.H. (1996), Evidence for the nutritional essentiality of boron. J. Trace Elem. Exp. Med., 9: 215-229. https://doi.org/10.1002/(SICI)1520-670X(1996)9:4<215::AID-JTRA7>3.0.CO;2-P

[1092] World Health Organization. Boron. In: Trace elements in human nutrition and health. Geneva, 1996.

[1093] Nielsen F. H. (1998). The justification for providing dietary guidance for the nutritional intake of boron. Biological trace element research, 66(1-3), 319–330. https://doi.org/10.1007/BF02783145

[1094] Medline (2020) 'Boron', NIH, Herbs and Supplements, Accessed Online Jan 04 2021: https://medlineplus.gov/druginfo/natural/894.html

[1095] Hooshmand, S., & Arjmandi, B. H. (2009). Viewpoint: dried plum, an emerging functional food that may effectively improve bone

health. Ageing research reviews, 8(2), 122–127. https://doi.org/10.1016/j.arr.2009.01.002

[1096] NIH (2020) 'Boron: Fact Sheet for Health Professionals', Dietary Supplement Fact Sheets, Accessed Online Jan 02 2021: https://ods.od.nih.gov/factsheets/Boron-HealthProfessional/

[1097] M R Naghii, P M Wall & S Samman (1996) The boron content of selected foods and the estimation of its daily intake among free-living subjects., Journal of the American College of Nutrition, 15:6, 614-619, DOI: 10.1080/07315724.1996.10718638

[1098] Pizzorno, Lara. “Nothing boring about boron.” Integrative Medicine: A Clinician’s Journal 14, no. 4 (2015): 35.

[1099] Richold M. (1998). Boron exposure from consumer products. Biological trace element research, 66(1-3), 121–129. https://doi.org/10.1007/BF02783132

[1100] Lee et al (2006). Effects of infrared radiation on skin photo-aging and pigmentation. Yonsei medical journal, 47(4), 485–490.

[1101] Wunsch, A., & Matuschka, K. (2014). A controlled trial to determine the efficacy of red and near-infrared light treatment in patient satisfaction, reduction of fine lines, wrinkles, skin roughness, and intradermal collagen density increase. Photomedicine and laser surgery, 32(2), 93–100.

[1102] "Kang et al (2020) ‘Near-infrared-emitting nanoparticles activate collagen synthesis via TGFβ signaling’ Sci Rep 10, 13309.

[1103] Kong et al (2015). A comparative study of the effects of retinol and retinoic acid on histological, molecular, and clinical properties of human skin. Journal of Cosmetic Dermatology, 15(1), 49–57. Portico.

[1104] Yang et al (2014). A randomized, double-blind, placebo-controlled study of a novel pantothenic Acid-based dietary supplement in subjects with mild to moderate facial acne. Dermatology and therapy, 4(1), 93–101.

[1105] Rembe et al (2018). Effects of Vitamin B Complex and Vitamin C on Human Skin Cells: Is the Perceived Effect Measurable?. Advances in skin & wound care, 31(5), 225–233.
[1106] Navarrete-Solís et al (2011). A Double-Blind, Randomized Clinical Trial of Niacinamide 4% versus Hydroquinone 4% in the Treatment of Melasma. Dermatology research and practice, 2011, 379173.
[1107] Ren et al (2007). Effects of selenium and iodine deficiency on bone, cartilage growth plate and chondrocyte differentiation in two generations of rats. Osteoarthritis and cartilage, 15(10), 1171–1177. https://doi.org/10.1016/j.joca.2007.03.013
[1108] Yan et al (2011). Fluoride induces apoptosis and alters collagen I expression in rat osteoblasts. Toxicology letters, 200(3), 133–138. https://doi.org/10.1016/j.toxlet.2010.11.005